β-Adrenoceptor Activity of the Stereoisomers of the Bufuralol Alcohol and Ketone Metabolites

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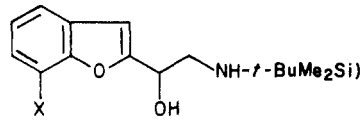
The stereoisomers of 2-[(*tert*-butylamino)methyl]-7-methyl-2,7-benzofurandimethanol (**2**) and 2-[2-(*tert*-butylamino)-1-hydroxyethyl]-7-benzofuranyl methyl ketone (**3**), the alcohol and ketone metabolites of bufuralol, have been prepared and examined for β-adrenoceptor activity in rats. All the stereoisomers with the *S* configuration hydroxylamine side chain showed potent β_2-antagonist activity comparable to (*S*)-bufuralol (**1a**). In contrast, a wide range of antagonist potencies was observed at the β_1-receptor; only alcohol diastereomer **9a** was more active than **1a**. This suggests that the shape of the 7-substituent in these benzofurans influences the degree of interaction with the β_1-receptor much more than with the β_2-receptor. Partial β_1-agonist activity was associated not only with all the stereoisomers with the *S* configuration hydroxylamine side chain but also with some of the *R* configuration derivatives, especially (*R*)-ketone **3b**. The results suggest that the margin of difference in β-adrenoceptor activity between compounds epimeric at the hydroxylamine side chain can be significantly influenced by a suitable substituent in the aromatic nucleus.

Bufuralol[1] (**1**) is a potent, nonselective β-adrenoceptor antagonist[2] with a β_2 partial agonist properties.[3,4] The drug has been proven very effective[5] in trials for the treatment of essential hypertension, and this activity has been attributed[4] to a favorable balance of β-blockade and β_2-agonist-mediated vasodilation.

The metabolism of bufuralol is complex; many metabolites are formed,[6] differential metabolism of the two enantiomers occurs,[7] and in a small percentage of subjects, differences due to genetic polymorphism are also encountered.[8] Nevertheless, only two metabolites, the alcohol **2** and to a lesser extent ketone **3**, are present in

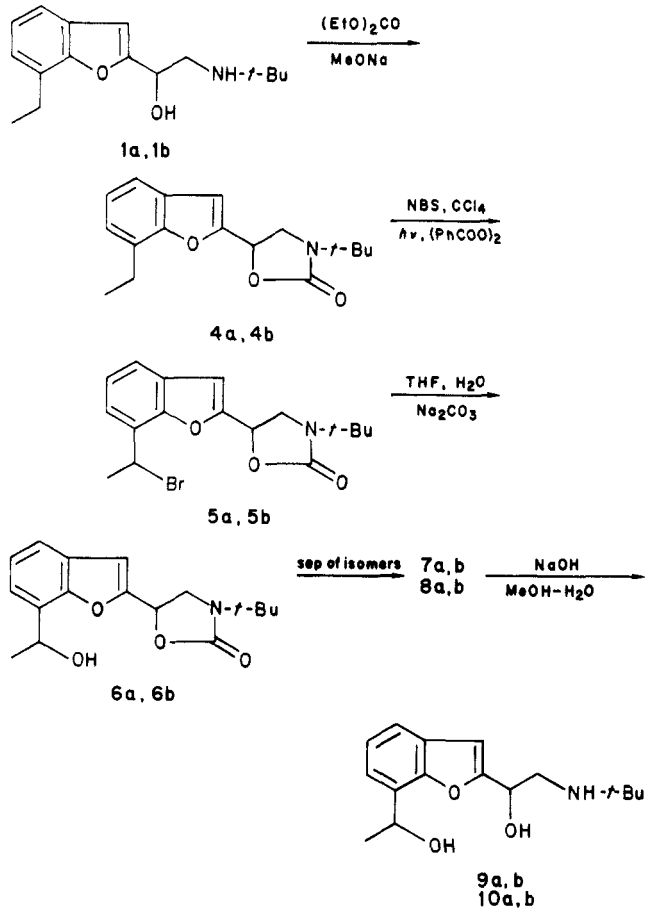


1, X = CH_2CH_3
2, X = $CHOHCH_3$
3, X = $COCH_3$

sufficient quantity and for sufficient duration to contribute[7] to the activity observed after bufuralol administration. While racemic mixtures of both **2** and **3** have been prepared previously and shown[9] to possess β-adrenoceptor activity, the individual isomers have not been available.

We set the following objectives as overall goals for this project at the outset: to synthesize all four alcohol diastereomers, to evaluate the biological activity of each isomer, to reanalyze the metabolite levels from man in terms of the individual isomers, to investigate the stereoselectivity of the metabolic hydroxylation, and, ultimately, to assess the true contribution of the metabolites to the overall effects seen with bufuralol. This paper describes the synthesis of the alcohol and ketone isomers and evaluation of their β-adrenoceptor antagonist and β_1 partial agonist activities in rats.

Scheme I[a]



[a] The a and b series represent the compounds with the *S* and *R* configuration ethanolamine side chains, respectively.

Chemistry. Bufuralol itself has been converted[10] into the racemic metabolites by a previously unpublished route. This method, shown in Scheme I, was applied separately

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(10) Osbond, J. M.; Wickens, J. C., unpublished results.

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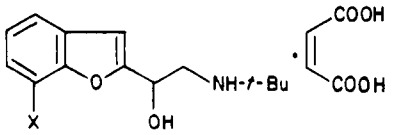
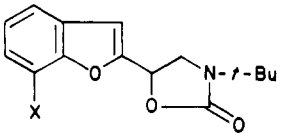
Table I. Benzofuranylethanolamines



compd[a]	X	mp, °C	cryst solvent	$[\alpha]^{20}D$ (MeOH, 1%), deg	yield, %	empirical formula	anal.	β-antagonism: ED_{50}, μg/kg: inhibn of tachycardia (β_1)	β-antagonism: ED_{50}, μg/kg: inhibn of depressor resp (β_2)	β-agonism: ED_{30}, μg/kg, inc in heart rate
(*S*)-bufuralol								169	13	53
(*R*)-bufuralol								>2000	>2000	>1000
9a	$CH(OH)CH_3$	122–125	EtOAc	−18.3	84	$C_{20}H_{27}NO_7$	C, H, N	46	9	0.7
9b	$CH(OH)CH_3$	128–130	EtOAc	+18.4	89	$C_{20}H_{27}NO_7$	C, H, N	>2000	>2000	>1000
10a	$CH(OH)CH_3$	135–138	MeCN	−56.6	53	$C_{20}H_{27}NO_7$	C, H, N	284	19	19
10b	$CH(OH)CH_3$	133–135	EtOAc	+56.0	85	$C_{20}H_{27}NO_7$	C, H, N	>2000	907	305
3a	$COCH_3$	166–169	MeCN	−42.3	57	$C_{20}H_{25}NO_7$	C, H, N	203	19	0.6
3b	$COCH_3$	166–169	MeCN	+38.2	65	$C_{20}H_{25}NO_7$	C, H, N	>2000	312	32
propranolol								71	42	>1000

[a] The **a** and **b** series represent the compounds with the *S* and *R* configuration ethanolamine side chains, respectively.

Table II. Oxazolidinone Intermediates



compd[a]	X	mp, °C	cryst solvent	$[\alpha]^{20}D$ (MeOH, 1%), deg	yield, %	empirical formula	anal.
4a	Et	75–76	methylcyclohexane	+82.9	89	$C_{17}H_{21}NO_3$	C, H, N
4b	Et	68–69	methylcyclohexane	−82.8	92	$C_{17}H_{21}NO_3$	C, H, N
7a	$CH(OH)CH_3$	131–132	EtOAc	+113.7	8.1	$C_{17}H_{21}NO_4$	C, H, N
7b	$CH(OH)CH_3$	131–132	EtOAc	−114.1	12.4	$C_{17}H_{21}NO_4$	C, H, N
8a[b]	$CH(OH)CH_3$			+34.0	9.1	$C_{17}H_{21}NO_4$	C, H, N
8b[b]	$CH(OH)CH_3$			−34.7	11.3	$C_{17}H_{21}NO_4$	C, H, N
11a	$COCH_3$	173–175	EtOAc	+76.0	73	$C_{17}H_{19}NO_4$	C, H, N
11b	$COCH_3$	174–175	EtOAc	−75.1	85	$C_{17}H_{19}NO_4$	C, H, N

[a] The **a** and **b** series represent the compounds with *S* and *R* configuration ethanolamine side chains, respectively. [b] Noncrystalline glass, purified by chromatography.

to each enantiomer[1] of bufuralol to give the optically active derivatives described herein. Protection of the ethanolamine function as the oxazolidinone **4** required base catalysis. Radical bromination effected functionalization to the bromoethyl derivatives **5** that were hydrolyzed to alcohols **6**. After an initial clean up, the mixture of alcohol diastereoisomers was separated by a combination of fractional crystallization and preparative liquid chromatography. Alkaline hydrolysis of the pure diastereomers **7** and **8** afforded target ethanolamines **9** and **10**, respectively.

The mixture of alcohols **6** was oxidized with pyridinium chlorochromate and deprotected to give ketones **3** (Scheme II). Final compounds and intermediates are detailed in Tables I and II, respectively.

In order to assess the degree to which enantiomer and/or diastereomeric impurities in each compound could contribute to the observed biological activities, we considered it important to define isomeric purity. The optical purity of the bufuralol enantiomers was conveniently established by HPLC of the oxazolidinones **4** using a chiral stationary phase according to the method recently published[11] for propranolol. We estimated that each compound contained less than 1% of its enantiomer. Since none of the subsequent chemistry employed could give rise to racemization of the ethanolamine side chain, this level of enantiomeric purity would have been carried through to the alcohol and ketone derivatives. HPLC analysis of the alcohols put diastereomeric purity at 98.7% or better. On this basis, we conclude that activity due to isomeric impurities would have been important only in those cases where the impurity was at least 100-fold more potent than the test compound in question. While it would be desirable to know the absolute configuration at both chiral centers, we have been unable to prepare crystals suitable for X-ray crystallography. In the absence of such evidence, we have presumed that, in common with other β-adrenergic agents,[12] the biologically active, levorotatory bufuralol enantiomer **1a** possesses the *S* configuration. Consequently, the **a** and **b** series represent the compounds with the *S* and *R* configuration ethanolamine side chains, respectively.

Pharmacology. Compounds were tested for β-adrenoceptor antagonist and partial agonist activities in anaesthetized rats as described previously.[13] The results for blockade are expressed as the dose of test compound required to inhibit by 50% the tachycardia (β_1) and vasodepressor response (β_2) produced by a submaximal dose of isoproterenol. The β_1-agonist activity is expressed as

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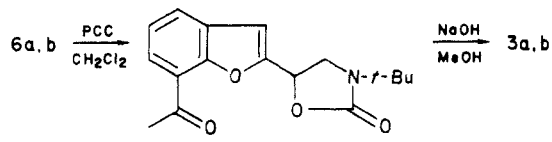
Scheme II[a]



11a, b

[a] The a and b series represent the compounds with the *S* and *R* configuration ethanolamine side chains, respectively.

the dose of test compound required to increase heart rate by 30 beats/min. The results are shown in Table I.

Discussion

Antagonism. Inspection of Table I reveals that, in accordance with the Easson–Stedman theory,[14] only those compounds with *S* configuration ethanolamine side chains were active β_1-antagonists. Of these, only alcohol **9a** exhibited improved potency over (*S*)-bufuralol. Since diastereomers **9a** and **10a** possess similar size, electronic properties, and overall lipophilicity, the ca. 6-fold difference in β_1-adrenoceptor antagonist activity between these two compounds most likely reflects the difference in absolute configuration of the 7-substituent. The shape of the 7-substituent plays a less critical role in determining activity at the β_2-receptor as all the new (*S*)-ethanolamines were roughly equivalent to (*S*)-bufuralol at this receptor type. Interestingly, (*R*)-ethanolamine **10b** and **3b** possessed weak β_2-antagonist activity.

Agonism. The most dramatic effects were seen on the β_1-agonist activity, wherein the (*S*)-ethanolamines **9a** and **3a** showed ca. 75–90-fold increase in potency over (*S*)-bufuralol. This strongly implies a receptor-activating role for the oxygenated 7-substituents. In contrast, the high level of activity was not maintained in diastereomer **10a**, presumably because the configuration of that hydroxyethyl group did not allow the favorable receptor interaction found in **9a** and **3a**. A parallel situation applies in the (*R*)-ethanolamine series. Thus, (*R*)-bufuralol and the alcohol with the unfavorable configuration of the 7-substituent, **9b**, were both inactive. However, alcohol **10b**, which has the favorable configuration of the 7-substituent found in **9a**, did show weak partial agonist activity. (*R*)-Ketone **3b** was even more potent than (*S*)-bufuralol in our tests for β-agonism.

On the basis of these results we conclude that in accordance with the Easson–Stedman theory superior adrenoceptor activity is shown by the compounds with the correct absolute configuration hydroxylamine side chains. However, the margin of difference in activity between the side-chain epimers can very considerably. For example, alcohol diastereomers **9a** and **10b** show a ca. 400-fold difference in partial agonist activity while ketones **3a** and **3b** show only a 16-fold difference in β_2-antagonist activity. The present study does not include β_2-agonist activity, but unpublished results[15] from our cat model[4] indicate that vasodilator effects are found in all the compounds irrespective of the ethanolamie side-chain configuration. Additionally, it has recently been reported[16] that both enantiomers of the β-adrenoceptor antagonist pindolol exhibit partial agonist activity. It would seem, therefore, that while the absolute configuration of the hydroxylamine side chain determines relative potency at β-adrenoceptors, absolute potency and the margin of difference in activity between side-chain epimers can be influenced significantly by the presence of a suitable substituent in the aromatic ring.

Experimental Section

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 782 spectrometer. NMR spectra were obtained on a Bruker WM-300 spectrometer with tetramethylsilane as internal reference. Optical rotations were obtained on a Perkin-Elmer 141MC polarimeter in methanol at 1% concentration. Each purified product had IR and NMR spectra compatible with its structure and was homogeneous by TLC. Microanalyses were within ±0.4% of the theoretical values for the elements measured. General workup procedures involved washing all organic extracts with water, drying over sodium sulfate, and filtering prior to evaporation. Chromatography was carried out with Merck silica gel 60.

(*S*)- and (*R*)-Bufuralol 1a and 1b. Bufuralol was resolved into its enantiomers with di-*p*-toluoyltartaric acid as described previously.[1]

3-*tert*-Butyl-5(*S*)- (4a) and 3-*tert*-Butyl-5(*R*)-(7-ethyl-2-benzofuranyl)-2-oxazolidinone (4b). A mixture of 16.6 g (64 mmol) of **1a** and 100 mL of diethyl carbonate was heated to reflux and then treated with portions of sodium methoxide (ca. 3 × 30 mg) at 15-min intervals until all the starting material had been consumed. The mixture was cooled, filtered, and evaporated, and the residue was recrystallized from methylcyclohexane to give 16.3 g (89%) of **4a**, mp 75–76 °C. Anal. ($C_{17}H_{21}NO_3$) C, H, N. The *R* isomer **4b** was prepared from **1b** in a similar fashion.

3-*tert*-Butyl-5(*S*)-[7-(1-hydroxyethyl)-2-benzofuranyl]-oxazolidinones 7a and 8a. A stirred solution of 16.3 g (57 mmol) of **4a**, 15.1 g (85 mmol) of *N*-bromosuccinimide, and 20 mg of dibenzoyl peroxide in 250 mL of carbon tetrachloride was illuminated with a 200-W lamp. The internal temperature was 52 °C. After 6 h the mixture was cooled, washed with water, and after workup, furnished 35 g of crude bromoethyl diastereomers **5a**. The dark brown oil was dissolved in 350 mL of 4:1 THF–water, and the solution was stirred at 60 °C for 24 h with the addition of small portions of sodium carbonate to neutralize the acid formed during the reaction. The solvents were evaporated, and the residue was partitioned between dichloromethane and water. Workup afforded a crude mixture of alcohols **6a** that was purified by chromatography, eluting first with 20% ethyl acetate–60–80 °C petrol to remove nonpolar impurities and then with 30% ethyl acetate–60–80 °C petrol to obtain the pure alcohols **6a**, 7.0 g (41%). The semisolids were triturated with ether and allowed to stand overnight at 0 °C to complete crystallization. The crystals were filtered off and recrystallized twice from ethyl acetate to give 1.4 g (8.1% based on **4a**) of **7a**, mp 131–132 °C. Anal. ($C_{17}H_{21}NO_4$) C, H, N. Isomeric pourity was assessed by analytical HPLC (10 × 0.4 cm, Hypersil 3 μm; 3% *i*-PrOH–hexane) and shown to be at least 98%. The crystallization residues containing the other diastereomer were combined and purified by preparative liquid chromatography (Waters Prep. 500 System; two silica cartridges [2 × 325 g]; 7% *i*-PrOH–hexane; 200 mL min^{-1}). Three cuts were made corresponding to material of >96%, 80–96%, and <80% purity with respect to isomer **8a**. The 80–96% fraction was recycled, and cuts were taken as above. The combined >96% fractions were evaporated and further purified on a small silica column (1% MeOH–CH_2Cl_2) to remove high-boiling paraffin impurities, affording 1.57 g (9.1% based on **4a**) of **8a**, as a noncrystalline glass. Anal. ($C_{17}H_{21}NO_4$) C, H, N. The remaining fractions from the preparative LC were combined, evaporated, and chromatographed to remove high boilers to give 1.89 g of mixed alcohols that were used in the preparation of ketone **11a**.

3-*tert*-Butyl-5(*R*)-[7-(1-hydroxyethyl)-2-benzofuranyl]-oxazolidinones 7b and 8b. The bromination–hydrolysis sequence was carried out on 14.25 g (50 mmol) of the (*R*)-oxazolidinone **4b** and gave the pure diastereomeric alcohols **6b** in 49% yield. Separation by crystallization and preparative LC as above afforded 1.87 g (12.4% based on **4b**) of **7b**, mp 131–132 °C [Anal. ($C_{17}H_{21}NO_4$) C, H, N (isomer purity by HPLC, 99%))], 1.71 g (11.3% based on **4b**) of **8b** as a noncrystalline glass [Anal. ($C_{17}H_{21}NO_4$) C, H, N (96% isomer purity)], and 2.45 g of mixed

(14) For a review see: Patil, P. N.; Miller, D. D.; Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323.
(15) Blaber, L. C.; Burden, D. T. unpublished results.
(16) Clark, B. J.; Bertholet, A. *Gen. Pharmacol.* **1983**, *14*, 117.

alcohols for use in the preparation of ketone **11b**.

2(*S*)-[(*tert*-Butylamino)methyl]-7-methyl-2,7-benzofurandimethanol–Maleic Acid (9a and 10a). A solution of 1.2 g (4 mmol) of oxazolidinone **7a** in 10 mL of 10 M KOH and 15 mL of methanol was heated under reflux for 18 h. The solvents were evaporated, and the residue was partitioned between water and dichloromethane. Workup afforded the free base which was converted to the maleate salt. Recrystallization from ethyl acetate gave 1.30 g (84%) of **9a** after drying at 110 °C in vacuo; mp 122–125 °C. Anal. ($C_{20}H_{27}NO_7$) C, H, N. Isomer purity was assessed by analytical HPLC (10 × 0.4 cm^{-1}; Hypersil 30D5; 60% MeOH–H_2O) after conversion to the *N*-isopropylurea derivative by reaction of the free base with a 3-fold excess of *N*-isopropyl isocyanate in dichloromethane for 1 h. The product contained 1.3% of diastereomer **10a** or its enantiomer **10b**. Similar hydrolysis of 1.34 g (4.4 mmol) of oxazolidinone **8a** afforded, after recrystallization from acetonitrile, 0.91 g (53%) of **10a**, mp 135–138 °C. Anal. ($C_{20}H_{27}NO_7$) C, H,N. This material contained 1.0% of diastereomer **9a** or its enantiomer **9b** by HPLC of the *N*-isopropylurea derivative.

2(*R*)-[(*tert*-Butylamino)methyl]-7-methyl-2,7-benzofurandimethanol–Maleic Acid (9b and 10b). Similar hydrolysis of 1.71 g (5.6 mmol) of **7b** afforded, after recrystallization from ethyl acetate and drying at 110 °C in vacuo, 1.98 g (89%) of **9b**, mp 128–130 °C. Anal. ($C_{20}H_{27}NO_7$) C, H, N. This material contained 1.0% of **10b** or its enantiomer **10a** by HPLC of the *N*-isopropylurea derivative. Similar hydrolysis of 1.50 g (5.0 mmol) of **8b** afforded, after recrystallization from ethyl acetate, 1.65 g (85;) of **10b**, mp 133–135 °C. Anal. ($C_{20}H_{27}NO_7$) C, H, N. This material contained 0.8% of **9b** or its enantiomer **9a** by HPLC of the *N*-isopropylurea derivative.

5(*S*)-(7-Acetyl-2-benzofuranyl)-3-*tert*-butyl-2-oxazolidinone (11a) and the 5(*R*) Isomer 11b. A solution of 1.89 g (6.2 mmol) of the residue of diastereomers from the preparative LC separation of **7a** and **8a** in 25 mL of dichloromethane containing 4 g of pyridinium chlorochromate was heated under reflux for 1 h. The liquid was decanted from the black tar and washed with 2 N NaOH followed by 2 N HCl. After workup, the crude residue was recrystallized from ethyl acetate to give 1.38 g (73%) of **11a**, mp 173–175 °C. Anal. ($C_{17}H_{19}NO_4$) C, H, N.

Similar treatment of 2.43 g (8.0 mmol) of the residue of diastereomers from the preparative LC separation of **7b** and **8b** afforded 2.05 g (85%) of **11b**, mp 174–175 °C. Anal. ($C_{17}H_{19}NO_4$) C, H, N.

2-[2-(*tert*-Butylamino)-1(*S*)-hydroxyethyl]-7-benzofuranyl Methyl Ketone–Maleic Acid (3a) and the 1(*R*) Isomer 3b. A solution of 1.18 g (3.9 mmol) of oxazolidinone **11a** in 10 mL of 10 M KOH and 30 mL of methanol was heated under reflux for 8 h. The solvents were evaporated, and the residue was partitioned between water and dichloromethane. Workup afforded the free base that was purified by filtration through silica with 10% MeOH–CH_2Cl_2 and was then converted to the maleate salt. Recrystallization from acetonitrile gave 0.87 g (57%) of **3a**, mp 166–169 °C. Anal. ($C_{20}H_{25}NO_7$) C, H, N.

Similar hydrolysis of 1.9 g (6.3 mmol) of oxazolidinone **11b** afforded 1.59 g (65%) of **3b**, mp 166–169 °C. Anal. ($C_{20}H_{25}NO_7$) C, H, N.

Pharmacological Methods. β-Adrenoceptor antagonism was measured in rats anaesthetized with pentobarbitone sodium (75 mg/kg ip). The rats were bilaterally vagotamized, and the trachea was cannulated. Isoproterenol (0.1 μg/kg) and test compounds dissolved in saline were administered through a polyethylene catheter into the right femoral vein, and the blood pressure was recorded from the left carotid artery by means of a Bell and Howell 4422 transducer connected to a Grass Model 79D recorder. Heart rate was recorded with a tachograph triggered from the arterial pulse. Five minutes after injection of isoproterenol, the test compound was injected, and heart rate and blood pressure were recorded. The procedure was repeated with cumulative doses of test compound up to a maximum dose of 2 mg/kg. The test was carried out in six rats for each compound, and the percentage blockade of both isoproterenol responses for each dose was calculated. The ED_{50} values (defined as the dose producing 50% reduction of the control isoprenaline response) and 95% confidence limits were calculated from the log dose–response relationship established by linear regression.[17] Statistical analysis of the results showed that the 95% confidence limits for the ED_{50} values averaged 30% (standard deviation 14%).

β-Adrenoceptor agonism was measured by the method of Barrett and Carter[18] in rats anaesthetized with pentobarbitone sodium (75 mg/kg ip) treated 20–24 h previously with reserpine (5 mg/kg ip). Single doses of test compound were administered into the tail vein, and up to 20 animals were used, depending on activity. Blood pressure and heart rate were recorded as above. A dose–response relationship was established, and an ED_{30} value (defined as the dose producing a 30 beats/min increase in heart rate) and 95% confidence limits were calculated as above. Statistical analysis of the results showed that the 95% confidence limits for the ED_{30} values averaged 60% (standard deviation 37%).

Acknowledgment. We thank D. T. Burden of the Pharmacology Department for the biological results, the Physical Methods Department for the microanalyses, optical rotations, and spectra, and M. J. B. Lloyd and S. A. Haq for the HPLC analytical and preparative work. We are grateful to J. C. Wickens for helpful discussions on the synthetic work.

Registry No. **1a**, 64100-62-5; **1b**, 64100-61-4; **3a**, 84952-24-9; **3a** maleate, 97858-38-3; **3b**, 84952-27-2; **3b** maleate, 97858-39-4; **4a**, 97733-04-5; **4b**, 97749-44-5; **5a** (isomer 1), 97733-05-6; **5a** (isomer 2), 97733-06-7; **5b** (isomer 1), 97733-07-8; **5b** (isomer 2), 97733-08-9; **7a**, 97733-09-0; **7b**, 97733-10-3; **8a**, 97749-27-4; **8b**, 97733-11-4; **9a**, 97805-54-4; **9a** maleate, 97805-56-6; **9b**, 97805-58-8; **9b** maleate, 97805-60-2; **10a**, 97805-55-5; **10a** maleate, 97805-57-7; **10b**, 97805-59-9; **10b** maleate, 97805-61-3; **11a**, 97733-12-5; **11b**, 97733-13-6; bufuralol, 54340-62-4.

Supplementary Material Available: Confidence limits for the biological test results (1 page). Ordering information is given on any current masthead page.

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