extracted with EtOAc (3 × 70 mL). The organic phase was dried ($MgSO_4$) and evaporated to give 10.7 g of a viscous oil, which was purified through its oxalate to yield 13 g of **21** recrystallized from 2-PrOH, mp 122 °C. Anal. ($C_8H_{17}NO_6$) C, H, N. **22** was prepared similarly using *t*-$BuNH_2$.

Preparation of Compounds 21 and 22. Procedure F. Compounds **21** and **22** were prepared by heating under reflux for 12 h a solution of epichlorohydrin (0.1 mol) with an excess of *i*-$PrNH_2$ or *t*-$BuNH_2$ in 100 mL of EtOH. The solvents were evaporated and the crystalline residue dissolved in 10% aqueous NaOH. Excess K_2CO_3 was added and the mixture was extracted with EtOAc (3 × 70 mL), dried over $MgSO_4$, and filtered. HCl gas was then bubbled through the EtOAc solution to afford the hydrochlorides **21** and **22**.

Preparation of Compound 13. Procedure G. To a solution of 3.81 g (12 mmol) of the maleate of **8** in 50 mL of MeOH was added 2.4 g of $NaBH_3CN$ in small portions. The pH was adjusted to 3–4 by 2 N HCl after each addition. The solution was stirred for 1 h and the MeOH was evaporated under reduced pressure (~30 °C). Excess K_2CO_3 was added and the mixture was extracted three times with EtOAc. The organic phase was dried and evaporated, and the residue was taken up in anhydrous ethyl ether. After filtration of excess $NaBH_3CN$, **13** (2 g) was obtained: IR 3400 (very broad, OH, NH), absence of imine bond near 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (m, 3 H), 3.20 (m, 1 H), 2.65 (m, ~4 H, 2-NH and N-CH_2), 1.1 (s, 9 H), 1.0 (d, $J \approx 6$ Hz, 6 H). The hydrochloride (2.1 g) was recrystallized from 2-PrOH: yield 1.6 g (46%); mp 181 °C. Anal. ($C_{10}H_{26}Cl_2N_2O_2$) C, H, N.

Adrenergic Receptor Agonists. Benzofuranylethanolamines

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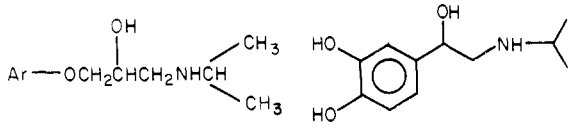
Two hydroxy-substituted benzofuranylethanolamines (**9** and **10**), analogues of adrenoceptor-active aryloxypropanolamines, were prepared and their β-adrenoceptor activity was examined. Compound **9** was found to be a β_1-selective adrenergic agonist with high intrinsic activity. Due to the rigidity of the benzofuranyl moiety of **9**, its functional groups cannot be brought into the same spatial positions as those of a phenylethanolamine-type agonist like isoprenaline. This could indicate that adrenergic agonists of the aryloxypropanolamine type and of the phenylethanolamine type are differently bound to the receptor when eliciting the effect.

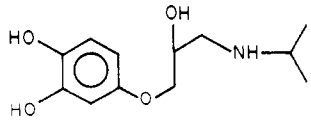
β-Adrenergic blocking agents in clinical use today are mostly aryloxypropanolamines of type **1**. Their β-blocking property is often combined with a β-agonistic activity,[1] and this receptor-stimulating effect is sometimes dominating, e.g., for compounds **2**[2] and **3**[3]. Recently, (*S*)-(−)-1-(4-hydroxyphenoxy)-3-(isopropylamino)-2-propanol (prenalterol; **4**) was described as a β_1-selective adrenoceptor agonist with an intrinsic activity slightly below that of isoprenaline.[4]



1

5

2, Ar = 3,4-$(OH)_2$-C_6H_4-
3, Ar = 2-thiazolyl
4, Ar = 4-OH-C_6H_5-



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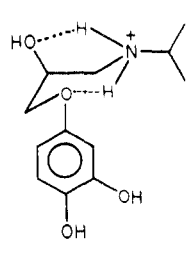

7

It is often suggested that adrenergic agonists like isoprenaline (**5**) are bound to the receptor via the phenolic OH groups, the OH group of the side chain, and the amino group. The aromatic nucleus and the isopropyl group may also participate in this respect.[5] The receptor is then triggered as a consequence of this multifunctional binding.

Adrenergic receptor agonists of the aryloxypropanolamine type like prenalterol (**4**) are assumed to bind to the same functional groups of the receptor as the phenylethanolamines, e.g., isoprenaline (**5**).[6] However, in the aryloxypropanolamines, the aromatic nucleus and the ethanolamine chain are separated by the $-OCH_2-$ moiety. Therefore, it is not obvious how the functional groups of the phenylethanolamines and the aryloxypropanolamines can occupy the same sites of the receptor.

To overcome this difficulty, folded conformations have been proposed in the literature. Comer[7] suggested that the β-adrenergic agonist activity of aryloxypropanolamines may be related to their ability to assume the folded conformation (**6**) which could be superimposed on the extended phenylethanolamine structure. Based on pharmacological results and NMR spectral data, Kaiser et al.[6,8] instead proposed a bicyclic conformation (**7**) that would

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Table I. Pharmacological Effects of the Compounds Tested

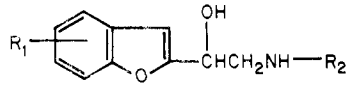
		effects on HR				effects on PR	
no.	n[a]	$K_B \pm$ SD, μmol/kg	n_{HR}[b]	intrinsic act., % of HR max	$K_A \pm$ SD (geom), μmol/kg	$K_B \pm$ SD, μmol/kg	n_{PR}[b]
4[c]	5			80	0.025 (0.019-0.031)		
9	3	0.34 ± 0.46	8	80 ± 7	0.21 (0.14-0.31)	1.12 ± 0.70	12
10	2	4.80 ± 3.71	5	27 ± 7	1.65 (1.60-1.70)	4.73 ± 2.17	4

[a] Number of animals used. [b] Number of K_B values on which the calculation of the mean weighed K_B is based. Each compound was tested at five dose levels and a calculated K_B value is obtained for each dose. The theoretical maximum number of K_B values is thus 15 for 9 and 10 for 10. [c] Previously published data; see ref 4.

satisfy the steric requirements of the receptor. Very recently, Zaagsma[9] presented spectral studies of aryloxypropanolamines that indicated that the bicyclic conformation proposed by Kaiser et al. was based on an incorrect interpretation of the spectral data.

In this paper, we present data indicating that agonists of the aryloxypropanolamine and the phenylethanolamine types may bind differently when triggering the receptor.

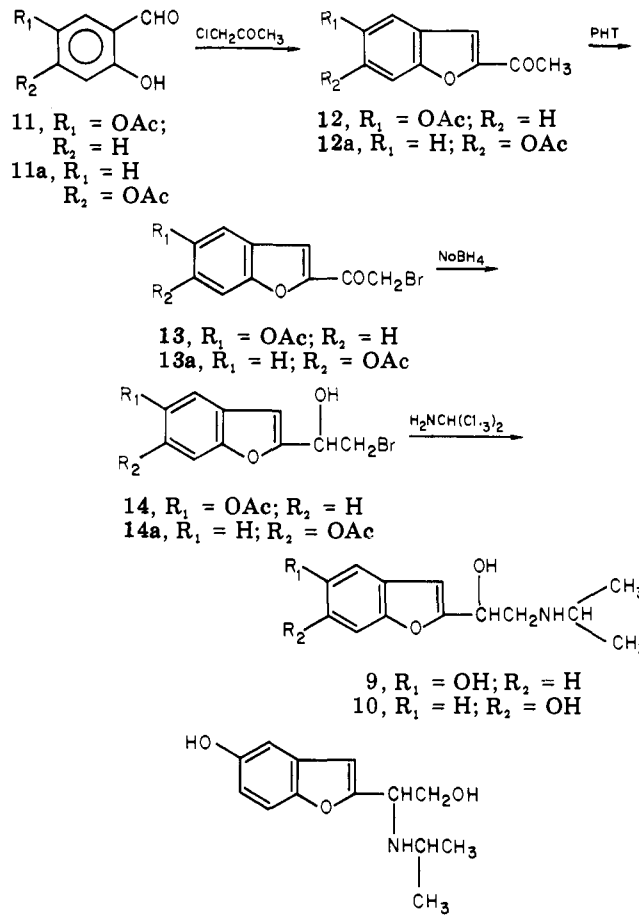
Bufuralol (8) is a potent β-receptor antagonist with some degree of intrinsic activity.[10,11] This structure has a particular interest, since it has a rigid structure from the aromatic nucleus over the ether function and up to and including the >CHOH group. Such a compound would be superimposable, for example, on the agonist 4 in its extended form but it is unable to assume the conformation of 6. It was thought that further information about the conformational arrangement in the interactions between adrenergic receptors and aryloxypropanolamine-type compounds could be obtained from compounds related to bufuralol, provided a potent agonist could be designed based on this structure. The two hydroxybenzofuranyl-2-ethanolamines 9 and 10 were, therefore, synthesized and their β-adrenergic activity was examined. Studies of molecular models indicate that the phenolic OH group of the benzofuran moiety should be either in position 5 or 6 to obtain maximum overlap with structure 4 and, therefore, compounds 9 and 10 were synthesized and tested.



8 (bufuralol), R_1 = 7-C_2H_5; R_2 = t-C_4H_9
9, R_1 = 5-OH; R_2 = i-C_3H_7
10, R_1 = 6-OH; R_2 = i-C_3H_7

Chemistry. The two benzofuranyl-2-ethanolamines 9 and 10 were prepared as illustrated in Scheme I. 5-Acetoxy-2-hydroxybenzaldehyde (11) was treated with chloroacetone under mild basic conditions, affording the methyl 2-benzofuranyl ketone 12. This was converted to the halomethyl ketone 13 using 2-pyrrolidinone hydrotribromide (PHT) as halogenating agent. Treatment of the product with $NaBH_4$ yielded the halohydrine 14. The ethanolamine 9 was then obtained from 14 using a large excess of isopropylamine. The alkylation reaction with isopropylamine yielded two isomeric products, 9 and 15, which could be separated by fractional crystallization. The product ratio 9:15 was influenced by the protection group used for the phenolic OH. It was thus found that when 1-[5-(benzyloxy)benzofuran-2-yl]-2-bromoethanol was treated with an excess of isopropylamine only the unwanted isomer corresponding to 15 could be isolated.

Scheme I



11, R_1 = OAc; R_2 = H
11a, R_1 = H; R_2 = OAc
12, R_1 = OAc; R_2 = H
12a, R_1 = H; R_2 = OAc
13, R_1 = OAc; R_2 = H
13a, R_1 = H; R_2 = OAc
14, R_1 = OAc; R_2 = H
14a, R_1 = H; R_2 = OAc
9, R_1 = OH; R_2 = H
10, R_1 = H; R_2 = OH

15

Protection of the phenol as its methyl ether was also attempted. In this case, however, demethylation using HBr or HI was unsuccessful.

Pharmacological Evaluation and Results. To determine the affinity of the compounds for the β_1- and β_2-adrenoceptor subtypes and the intrinsic activity on any one of these receptors, the study was performed using a pharmacological model offering one β_1- and another β_2-mediated effector. The positive chronotropic changes of the heart are controlled mainly by a β_1-adrenoceptor mechanism,[12,13] while the vasodilating mechanism of the peripheral precapillary resistance vessels is mediated mainly by β_2 adrenoceptors.[12] Heart rate and peripheral vascular resistance in the reserpinized, vagotomized cat were therefore chosen as β_1- and β_2-mediated variables, respectively, and compounds 9 and 10 were tested as described under Experimental Section. The K_B values for

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antagonistic effect on heart rate and peripheral vascular resistance, the intrinsic activities, and the K_A values for agonistic effects on heart rate are shown in Table I.

It is evident that both compounds **9** and **10** exhibit a certain affinity for both receptor types regarding β-adrenoceptor antagonistic properties. Compound **10** was found to have the same potency regarding cardiac and vascular β-adrenoceptor blocking effects, while **9** exhibits about three times higher affinity for the cardiac than for the vascular β-adrenoceptors. It is also evident from Table I that both compounds exert an intrinsic activity on the cardiac β adrenoceptors. Compound **9** is a more powerful positive chronotropic agent, with about eight times higher affinity than **10**. Also, the intrinsic activity of **9** is higher than that of **10** (80 ± 7 and 27 ± 7% of that of isoprenaline, respectively). The intrinsic activity of **9** is thus similar to that of prenalterol (**4**),[4] although the affinity of **9** is about one-eighth that of **4**.

Neither of the compounds were found to exhibit any peripheral vasodilatory property. The β adrenoceptors in the vascular bed have been characterized mainly as β_2 adrenoceptors[12] and have also been shown to be pharmacologically identical with the β-adrenoceptors mediating a decrease in airway resistance in the cat.[14] Based on this and on the fact that cardiac β-adrenoceptors are mainly of the β_1 type,[12,13] compounds **9** and **10** may be characterized as β_1-selective adrenoceptor agonists.

The supramaximal isoprenaline dose (2.0 nmol/kg of body weight) induced an increase in heart rate from 165 ± 6 to 256 ± 6 beats per minute and a decrease in perfusion pressure of the cats' hind leg from 102 ± 10 to 42 ± 4 mmHg, calculated from five experiments. Compound **9** (11.0 μmol/kg of body weight) maximally elevated the heart rate from 170 ± 12 to 243 ± 12 beats per minute. The corresponding values for compound **10** (12.5 μmol/kg of body weight) were 156 ± 1 and 181 ± 1 beats per minute, respectively.

Discussion

The pharmacological evaluation showed that **9** is a cardioselective adrenergic agonist with high intrinsic activity. This molecule can thus activate the adrenergic receptor, although it can not assume a conformation similar to **6**. The data therefore support the conclusion by Kaiser et al.[8] that aryloxypropanolamines do not assume conformations of type **6** when interacting with the receptor.

From studies of molecular models of, for example, isoprenaline (**5**) and **9** it is obvious that when the ethanolamine chains of the two compounds are superimposed the aromatic nucleus of **9** can not be brought into the same spatial position as that of the phenylethanolamine **5**. Due to the structural similarities between **4** and **9**, it can be assumed that also other aryloxypropanolamines differ from the spatial arrangement of the phenylethanolamines when triggering the receptor. It is also interesting to note that **9**, the most active of the two compounds studied here, has the hydroxy group in the para position with respect to the furan oxygen. This contrasts to the classical observations on monohydroxyarylethanolamines where the meta position for the hydroxyl group is favorable. This could indicate that the adrenergic receptor has several functional groups at the active site that can participate in the binding of the agonist when activating the receptor. Another possibility is that the same functional groups participate in the two cases and that the receptor has a certain flexibility and can adapt the positions of its functional groups to fit the phenylethanolamine as well as the aryloxypropanolamine type of agonist.

Experimental Section

Melting points were taken on a Mettler FPI apparatus. IR spectra were measured on a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded with a Varian CFT 20 instrument. $CDCl_3$ solutions were used with Me_4Si as internal standard unless otherwise stated. Mass spectral analysis was carried out with an LKB 9000 instrument at 70 eV.

Elemental analyses were performed by the Microanalytical Laboratory at the Institute for Agriculture, Uppsala. The analytical results obtained were within ±0.4% of the theoretical values. IR, NMR, and mass spectra were in all cases in accordance with expected data. Thin-layer chromatography (TLC) on silica gel plates were used to follow the reactions and to control the purity of the products.

5-Acetoxy-2-hydroxybenzaldehyde (**11**). This compound was prepared according to literature procedures.[15]

2,4-Diacetoxybenzaldehyde. This compound was prepared from 2,4-dihydroxybenzaldehyde using acetic anhydride as described for the acetylation of 2,5-dihydroxybenzaldehyde:[15] mp 64–65 °C (from EtOH), reported[16] 69 °C.

4-Acetoxy-2-hydroxybenzaldehyde (**11a**). The above diacetate (30 g, 0.135 mol) dissolved in 100 mL of acetone was stirred with 2 N NaOH (67.5 mL, 0.135 mol) at room temperature. After an 8-min reaction time, the alkaline solution was neutralized with concentrated HCl and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4), and the solvent was evaporated: yield 14.7 g (61%); mp 49–50 °C (from EtOH). Anal. ($C_9H_8O_4$) C, H.

Methyl 5-Acetoxy-2-benzofuranyl Ketone (**12**). Chloroacetone (14.3 g, 0.15 mol) was added slowly over 10 min to a stirred mixture of **11** (27.4 g, 0.15 mol) and anhydrous potassium carbonate (24.8 g, 0.18 mol) in 150 mL of acetonitrile. The mixture was stirred and refluxed until the reaction was complete as shown by TLC (ca. 1.5 h) and then filtered. The potassium carbonate was washed with chloroform, and the combined solvents were evaporated. Absolute ethanol was added to the residue and the product crystallized upon cooling. A second crop was obtained from the concentrated mother liquor, giving a total yield of 12.1 g (40%), mp 107–108 °C (from EtOH). Anal. ($C_{12}H_{10}O_4$) C, H.

Methyl 6-Acetoxy-2-benzofuranyl Ketone (**12a**). This compound was prepared from 4-acetoxy-2-hydroxybenzaldehyde as described for **12**: yield 10.8 g (33%); mp 99–101 °C (from EtOH). Anal. ($C_{12}H_{10}O_4$) C, H.

Bromomethyl 5-Acetoxy-2-benzofuranyl Ketone (**13**). A mixture of **12** (11.0 g, 0.05 mol), 2-pyrrolidinone hydrotribromide (PHT; 27.0 g, 0.05 mol), and 2-pyrrolidinone (4.7 g, 0.05 mol) in THF (100 mL) was heated under reflux for 2 h. The solution was cooled to 10 °C and filtered. After evaporation, a crystalline residue was obtained: yield 11.1 g (75%); mp 81–82 °C (from EtOH). Anal. ($C_{12}H_9BrO_4$) C, H.

Bromomethyl 6-Acetoxy-2-benzofuranyl Ketone (**13a**). This compound was prepared from methyl 6-acetoxy-2-benzofuranyl ketone as described for **13**: yield 5.0 g (34%); mp 120–121 °C (from EtOH). Anal. ($C_{12}H_9BrO_4$) C, H.

(±)-1-(5-Hydroxy-2-benzofuranyl)-2-(isopropylamino)-ethanol (**9**). Compound **13** (5.9 g, 0.02 mol) was dissolved in 50 mL of dioxane and 10 mL of water. Sodium borohydride (0.6 g, 0.015 mol) was added portionwise over 0.5 h, with stirring and cooling in ice. The reaction mixture was stirred at 20 °C for 2 h, whereupon the solvent was evaporated, water was added to the residue, and the mixture extracted with ether. The ether extract was washed with water, dried (Na_2SO_4), and evaporated to yield 5.3 g of an orange syrup of **14**. This crude product was refluxed with isopropylamine (10.6 g, 0.18 mol) in 75 mL of acetonitrile for 16 h. The solvent was then evaporated and 2 N HCl was added. The solution was extracted with ether and the extract discarded. The acidic solution was then neutralized using 10 N NaOH and again extracted with ether. This ether extract was

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washed with water and dried (Na_2SO_4), and the solvent was evaporated. The residue was taken up in EtOAc and the desired product crystallized from this solution upon cooling: yield 1.6 g (38%); mp 154–155 °C (from EtOAc); NMR (CD_3COCD_3) 7.19 (d, 1 H, J = 8.8 Hz, C_7 H), 6.91 (d, 1 H, J = 2.5 Hz, C_4 H), 6.78 and 6.68 (dd, 1 H, J = 8.8 and 2.5 Hz, C_6 H), 6.55 (br s, 1 H, C_3 H), 4.87–4.68 (m, 1 H, CHO*H*), 3.05–2.72 [m, 3 H CCH_2N and $-CH(CH_3)_2$], 1.05 ppm [d, 6 H, $-CH(CH_3)_2$]; MS m/z (relative intensity) 235 (1, M^+), 217 (1), 163 [5, $M - CH_2NHCH(CH_3)_2^+$], 147 (3), 105 (2), 72 [100, $CH_2NHCH(CH_3)_2^+$]. Anal. ($C_{13}H_{17}NO_3$) C, H, N.

When the mother liquor was concentrated and cooled, a second crop of crystals was obtained consisting of the isomeric 2-(5-hydroxy-2-benzofuranyl)-2-(isopropylamino)ethanol (**15**): yield 0.5 g (12%); mp 158–160 °C (from acetone); NMR (CD_3COCD_3) 7.22 (d, 1 H, J = 8.8 Hz, C_7 H), 6.91 (d, 1 H, J = 2.5 Hz, C_4 H), 6.77 and 6.67 (dd, 1 H J = 8.8 and 2.5 Hz, C_6 H), 6.56 (br s, 1 H, C_3 H), 4.04–3.47 [m, 3 H, CCH_2OH and $-CH(CH_2OH)NH-$], 2.84 [septet, 1 H, $-CH(CH_3)_2$], 1.07 and 0.99 ppm [dd, 6 H, $-CH(CH_3)_2$]; MS m/z (relative intensity) 204 (71, $M - CH_2OH^+$), 162 (47), 147 (7), 105 (7), 101 (24), 44 (100).

(±)-1-(6-Hydroxy-2-benzofuranyl)-2-(isopropylamino)-ethanol (10). This compound was prepared as described for **9**. The crude product was chromatographed on a silica gel column eluted with chloroform with increasing amounts of MeOH. This yielded the pure product in approximately 10% yield, mp 110–111 °C (from EtOAc/ether). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

Pharmacology. Cats of both sexes, weighing between 2.6 and 3.2 kg, were starved for 24 h and pretreated with reserpin (Serpasil, 2.5 mg/mL, 5 mg/kg of body weight) 18 h before experimentation in order to provoke neuronal noradrenaline depletion. The animals were anesthetized by a pentobarbital (Mebumal, 60 mg/mL ACO) injection (30 mg/kg of weight) intraperitoneally and maintained at a constant level of anesthesia by means of a continuous infusion of sodium pentobarbital [Mebumal, 0.1 (mg/min)/kg of body weight]. Artificial respiration was given by means of a respiratory pump (Braun) connected to a tracheal cannula.

The cats were vagotomized bilaterally, and the right carotid artery was catheterized for recording of the mean arterial blood pressure via a Statham P 23 strain gauge pressure transducer. The heart rate was recorded via a Grass 7P4 Cardiotachograph, which was triggered by the blood pressure oscillations.

The pharmacological effects on the peripheral vascular resistance in one hind leg were estimated as follows: the left femoral artery was cut and both ends were reconnected via a plastic catheter loop, which was passed through a peristaltic pump (Watson Mallow) delivering a constant flow of >10 mL/min. The hind leg was thus perfused with the cat's own blood at a constant flow rate. Alterations in vascular resistance measured as changes in perfusion pressure were recorded via a Statham P23 strain gauge pressure transducer connected to the loop distal to the roller pump. The left jugular and right femoral veins were catheterized for barbiturate and test compound administration, respectively.

All recordings were made on a Grass 7D polygraph. The blood gas status and hematocrit values of the animal were controlled continuously throughout the experiment and were regarded as normal within the following ranges: pH, 7.38 ± 0.06; pCO_2, 30.7 ± 1.4 mmHg; HCO_3, 19.0 ± 1.0 mequiv/L; hematocrit, 30 ± 10%.

A standard fluid therapy (Ringer acetate, ACO, 20 mL/kg body weight, + Macrodex, Pharmacia, 5 mL/kg of body weight, infused at 0.5 mL/min) was used to compensate for the fluid loss due to the reserpine pretreatment. Maximal heart rate and peripheral vascular effects were obtained at iv and ia injection of supramaximal doses of isoproterenol (IPR).

The test compounds were infused iv for 10 min at a rate of 1.0 mL/min in five stepwise raised concentrations. Each infusion was followed by an iv and an ia injection of IPR in concentrations which in the absence of test compounds induced control responses equal to about 80% of the maximal IPR effects.

Knowing that the submaximal IPR concentration used induces a response which may be identified at the top of the linear part of the IPR dose–response graph and assuming that any antagonistic property of the test compound represents a perfectly competitive interaction with IPR at the receptor site, any decrease in the response to the IPR standard concentration will reflect a parallel rightward shift of the IPR dose–response curve.

Dissociation constants characteristic of the affinity for the receptors were calculated for agonistic (K_A) and antagonistic (K_B) effects of the test compounds.

The doses of the test compounds producing semimaximal excitatory effects on the heart rate were taken as estimates of K_A. The K_B values for antagonistic effects on heart rate and peripheral vascular dilatation were calculated according to Åblad et al.[17]

The formula used provided us with a series of K_B values, one for each dose of test compound, in every experiment. These values which theoretically should be identical with each other within one experiment were, however, widely scattered due to a possible nonlinearity of the dose–response curve segment at its extreme points (i.e., around the 20–30 and the 70–80% level). For calculation of the "mean" K_B of each experiment, a "weighing" formula[17] was used.

Acknowledgment. We thank Drs. Peder Berntsson and Arne Brändström for valuable discussions, Hans Thorin for the mass spectra, and Mrs. Anita Niklasson for help with the silica gel chromatography.

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Synthesis and Antineoplastic Activity of Hydroquinone Dialdehydes

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A number of hydroquinone dialdehydes and structurally related compounds were synthesized and tested for antineoplastic efficacy against transplanted murine tumors. 3,6-Dihydroxy-4,5-dimethylphthalaldehyde, 3,6-dihydroxy-4,5-dipropylphthalaldehyde, and 3,6-dihydroxy-4,5-dimethylphthalaldehyde hemialdal tetraacetate significantly prolonged the survival time of mice bearing either Sarcoma 180, Ehrlich carcinoma, or adenocarcinoma 755 ascites tumors. In addition, these agents were cytotoxic to Sarcoma 180 cells in culture at concentrations in the range of 25–30 μM.

Several α,β-unsaturated aldehydes,[1-3] α-ketoaldehydes,[4-6] and periodate oxidation products of ribonucleosides[7,8] have been demonstrated to possess antineoplastic activity against experimental murine tumors. The biochemical

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