of exposure to aerosolized drug. The effects on LTC-, LTD-, PAF-, and histamine-induced bronchoconstriction were also evaluated by using techniques similar to those described for LTE except that maximally constrictory doses of LTC (50 μg/kg), LTD (50 μg/kg), PAF (10 μg/kg), and histamine (50 μg/kg) were employed.

For determination of the relative potency (IC_{50} values) of drugs delivered by this route, varied percentage concentrations of test drug were administered via the nebulizer. For determination of the time course of inhibition for various drugs, the animals were exposed for 5 min to a 1% concentration of drug, and the time to challenge with LTE was varied from 30 s to 5, 10, 30, 60, or 90 min. The change in tracheal pressure was averaged for three control and five drug-treated animals and the percent inhibition at each aerosol concentration was calculated. The median inhibitory concentrations (IC_{50} values) were determined from linear regression calculated by log concentration–response curves generated by at least three concentrations that caused inhibitory effects between 10% and 90%. The correlation coefficient for the regression line of each antagonist was always greater than 0.95. The duration of activity was calculated as the time when inhibition decreased to 40%.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determination of the spectral and analytical data and Marilyn Satchwell for her able assistance in preparation of the manuscript. We appreciate the guidance and encouragement of Dr. R. W. Kierstead during the course of this work.

Registry No. **5**, 79558-07-9; **6**, 40786-69-4; **7**, 88420-24-0; **8**, 88420-31-9; **9**, 88420-36-4; **10** (X = $(CH_2)_5$, n = 3, R = Et), 88420-45-5; **10** (X = $(CH_2)_3$, n = 1, R = Et), 88420-25-1; **10** (X = $(CH_2)_3$, n = 3, R = Et), 88420-32-0; **10** (X = $(CH_2)_3$, n = 5, R = Me), 88420-37-5; **10** (X = $(CH_2)_5$, n = 1, R = Et), 88420-28-4; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 1, R = Et), 104835-61-2; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 3, R = Et), 104835-62-3; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 5, R = Me), 104835-63-4; **10** (X = $(CH_2)_2[O(CH_2)_2]_2$, n = 1, R = Et), 88420-44-4; **10** (X = $(CH_2)_2[O(CH_2)_2]_2$, n = 3, R = Et), 104835-64-5; **10** (X = $(CH_2)_2[O(CH_2)_2]_3$, n = 1, R = Et), 104835-65-6; **10** (X = $CH_2)_3O(CH_2)_3$, n = 1, R = Et), 88420-46-6; **10** (X = $(CH_2)_3O(CH_2)_3$, n = 3, R = Et), 88420-47-7; **10** (X = $(CH_2)_4O(CH_2)_4$, n = 1, R = Et), 104835-66-7; **11**, 88420-23-9; **12**, 88420-04-6; **13**, 88420-07-9; **14**, 88420-01-3; **15**, 88420-14-8; **16**, 88420-06-8; **17**, 88420-10-4; **18**, 88420-12-6; **19**, 88420-11-5; **20**, 88420-20-6; **21**, 88420-13-7; **22**, 88420-15-9; **23**, 88420-16-0; **24**, 88420-17-1; **25**, 88419-74-3; **26**, 88419-79-8; **27**, 88419-82-3; **28**, 88419-76-5; **29**, 88419-89-0; **30**, 88419-81-2; **31**, 88419-85-6; **32**, 88419-86-7; **34**, 88419-95-8; **35**, 88419-88-9; **36**, 88419-90-3; **37**, 88419-91-4; **38**, 88419-92-5; **39**, 95265-23-9; **39** (R′ = OH), 72836-76-1; **40**, 95265-24-0; **41**, 95265-27-3; **42**, 95265-25-1; **43** (X = $(CH_2)_3$, R = Ac, n = 1), 101463-93-8; **43** (X = $(CH_2)_3$, R = H, n = 1), 104835-67-8; **43** (X = $(CH_2)_5$, R = Ac, n = 1), 101463-96-1; **43** (X = $(CH_2)_3$, R = H, n = 3), 104835-68-9; **43** (X = $(CH_2)_3$, R = Ac, n = 3), 101464-01-1; **44**, 104835-58-7; **45**, 101463-94-9; **46**, 101463-97-2; **47**, 104835-59-8; **48**, 101464-02-2; **49**, 84701-83-7; **50**, 101463-95-0; **51**, 101463-98-3; **52**, 104835-60-1; **53**, 101464-03-3; $Br(CH_2)_2O(CH_2)_2Br$, 5414-19-7; $Br(CH_2)_2O(CH_2)_2O(CH_2)_2Br$, 31255-10-4; $Br(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2Br$, 31255-26-2; $Br(CH_2)_3O(CH_2)_3Br$, 58929-72-9; $Br(CH_2)_4O(CH_2)_4Br$, 7239-41-0; ethyl 4-bromobutyrate, 2969-81-5; 1,5-dibromopentane, 111-24-0; 2,7-dihydroxynaphthalene, 582-17-2; methyl bromoacetate, 96-32-2; acetyl chloride, 75-36-5; 1,3-dibromopropane, 109-64-8; ethyl bromoacetate, 105-36-2; methyl 6-bromohexanoate, 14273-90-6.

Conformationally Defined Adrenergic Agents. 4. 1-(Aminomethyl)phthalans: Synthesis and Pharmacological Consequences of the Phthalan Ring Oxygen Atom

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The synthesis of a series of 1-(aminomethyl)phthalans **1b** is reported. The radioligand binding to α_1- and α_2-receptors and the in vitro pharmacology in α_1 (rabbit aorta) and α_2 (phenoxybenzamine-pretreated dog saphenous vein) tissues were determined and were compared to the activity of the corresponding 1-(aminomethyl)indans. The activity of this series of phthalans was found to be consistent with the electrostatic repulsion hypothesis that was used to design the parent indan (ERBCOP) compounds.[1] The effect of the phthalan ring oxygenation was to somewhat improve α_1-receptor potency relative to the 6-ERBCOP indans without having a general effect on the α_2-receptor potency. We conclude from the overall pattern of activity that while the norepinephrine type β-hydroxyl group may be beneficial for binding to the α_1-adrenoceptor, it is not required for strong binding to or full stimulation of the α_2-adrenergic receptor, provided that the conformational mobility associated with the phenylethylamine is restricted and maintained in a favorable conformation for receptor interaction.

We have previously[1] reported the synthesis and the α-adrenergic activity associated with a series of (aminomethyl)tetralin and (aminomethyl)indan derivatives (Figure 1, **1a**). These compounds were designed around a hypothesis we formulated that accounts for the adrenergic selectivity associated with 2- and 6-fluoronorepinephrines (FNEs)[2] on the basis of a conformational preference induced by an electrostatic repulsion between the aromatic fluorine atom and the side-chain hydroxyl group. These (aminomethyl)tetralins and (aminomethyl)indans (designated: electrostatic repulsion based conformational prototypes, ERBCOPs) were shown to exhibit α-adrenergic selectivity. In particular, the 6-ERBCOPs were highly α_2 selective with the greatest α_2 selectivity being seen for the 6-ERBCOP (aminomethyl)indan derivatives having nitrogen substituents no larger than methyl.

Having found these 6-ERBCOP compounds to have strong affinity and good selectivity for the α_2-adrenoceptor in radioligand binding assays, we decided to investigate the effects of reintroduction of the oxygen atom of the norepinephrine (NE) side-chain β-hydroxyl group. A number of reports have appeared that have indicated the importance of the benzylic hydroxyl group of phenethylamines interacting at α_1[3] and α_2-adrenergic receptors.[4-6]

(1) DeBernardis, J. F.; Kerkman, D. J.; Winn, M.; Bush, E. N.; Arendsen, D. L.; McClellan, W. J.; Kyncl, J. J.; Basha, F. Z. *J. Med. Chem.* **1985**, *28*, 1398.
(2) Kirk, K. L.; Cantacuzene, D.; Nimitkitpaisan, Y.; McCulloh, D.; Padgett, W. L.; Daly, J. W.; Creveling, C. R. *J. Med. Chem.* **1979**, *22*, 1493.
(3) Patil, P. N.; Miller, D. D.; Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323.
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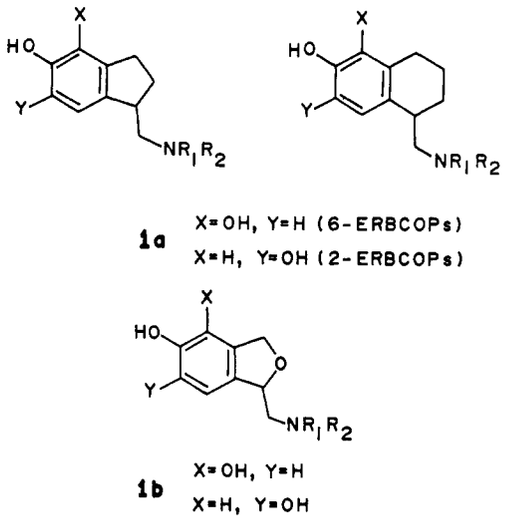


Figure 1.

It was of interest to us to investigate incorporation of an oxygen atom into the carbocyclic ring of the 2- and 6-ERBCOP compounds since, unlike the previously reported phenethylamine derivatives, these compounds are conformationally more restricted while lacking a benzylic oxygen atom or equivalent. However, the 6-ERBCOP derivatives possess significant α_2-receptor affinity and selectivity.[1] We reasoned that if this NE hydroxyl group interacts with the α_1- or α_2-receptor by acting as a hydrogen bond acceptor as well as a hydrogen bond donor, we should be able to mimic the hydrogen bond acceptor function by including an oxygen atom[7] within the carbocyclic ring of the 2- or 6-ERBCOP compounds (Figure 1, **1b**). We felt that a hydrogen bonding interaction of this sort would improve the affinity and possibly the selectivity of these compounds for the various adrenergic receptors.

The decision to place the oxygen atom within the ring was based on our intent to have it mimic the role of the NE hydroxyl group. Illustrated in Figure 2[8] is 6-FNE, shown in a conformation that is stabilized by the electrostatic repulsion between the aromatic fluorine atom and the side-chain hydroxyl group. It was this conformation that lead us to design the 6-ERBCOP compounds, and reintroduction of an oxygen atom into the 6-ERBCOP compounds could occur at the position of the methine hydrogen or the ring methylene. As can be seen in Figure 2, substitution of an oxygen atom for the ring methylene of the 6-ERBCOP compounds to give **1b** most closely approximates the position occupied by the oxygen atom of the 6-FNE side-chain hydroxyl group in its electrostatic repulsion-stabilized conformation.

In this paper we report the synthesis of a series of (aminomethyl)phthalan derivatives of general structure **1b**. The α_1- and α_2-radioligand binding affinities of these phthalans are compared with the affinities that have been previously reported[1] for the corresponding 6-ERBCOP compounds. In addition, we report the in vitro tissue pharmacology of phthalans **1b** and compare this to the previously unpublished in vitro activity of the 6-ERBCOP compounds.

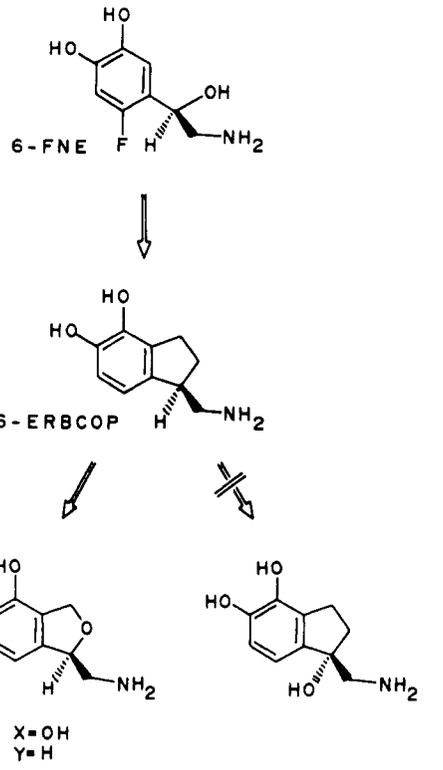
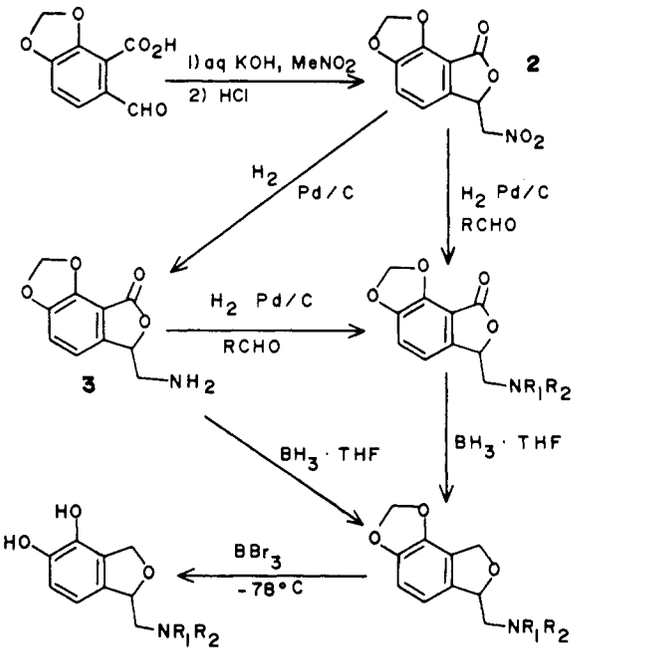


Figure 2.

Scheme I



5	$R_1 = R_2 = H$	**4**	$R_1 = R_2 = H$
8	$R_1 = R_2 = Me$	**6**	$R_1 = R_2 = Me$
9	$R_1 = R_2 = n\text{-}Pr$	**7**	$R_1 = R_2 = n\text{-}Pr$
12	$R_1 = Me, R_2 = H$	**10**	$R_1 = Me, R_2 = CH_2Ph$
		11	$R_1 = Me, R_2 = H$

Chemistry

The synthesis of the 4,5-disubstituted (aminomethyl)-phthalan derivatives is illustrated in Scheme I. Starting with 2,3-(methylenedioxy)-6-formylbenzoic acid,[9] 1-(nitromethyl)-4,5-(methylenedioxy)phthalide (**2**) was pre-

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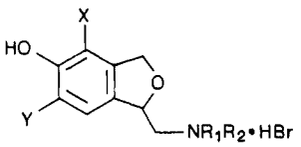
(8) A single enantiomer is shown only for clarity. The compounds were tested as racemates.

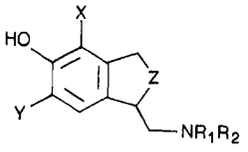
(9) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

Table I. Catecholamines Prepared for This Study



compd	X	Y	R_1	R_2	mp, °C	formula	anal.
5	OH	H	H	H	218–220	$C_9H_{12}BrNO_3$	C, H, N
8	OH	H	CH_3	CH_3	190–192	$C_{11}H_{16}BrNO_3$	C, H, N
9	OH	H	*n*-Pr	*n*-Pr	105–107	$C_{15}H_{24}BrNO_3 \cdot 1/2\ H_2O$	C, H, N
12	OH	H	CH_3	H	221–222	$C_{10}H_{14}BrNO_3$	C, H, N
13	H	OH	H	H	237–238	$C_9H_{12}BrNO_3$	C, H, N

Table II. Radioligand Binding Data[a] for the Phthalan and Corresponding Indan[b] Compounds



compd	X	Y	Z	R_1	R_2	K_i α_1 (90% CL)[c]	K_i α_2 (90% CL)[c]
5	OH	H	O	H	H	9800 (8200–11800)	77 (52–115)
8	OH	H	O	CH_3	CH_3	1160 (610–2200)	10.7 (6.8–16.6)
9	OH	H	O	*n*-Pr	*n*-Pr	10300 (3090–34700)	670 (180–2600)
12	OH	H	O	CH_3	H	1970 (1200–3100)	18 (11–28)
13	H	OH	O	H	H	99000 (14000–710000)	13000 (370–48000)
14[b]	OH	H	CH_2	H	H	2250 (1500–3350)	15 (10–24)
15[b]	OH	H	CH_2	CH_3	CH_3	6900 (3900–12000)	25 (18–37)
16[b]	OH	H	CH_2	*n*-Pr	*n*-Pr	7400 (2700–20500)	470 (280–770)
17[b]	OH	H	CH_2	CH_3	H	2000 (990–4100)	7 (4–13)
18[b]	H	OH	CH_2	H	H	26000 (19000–35000)	520 (260–1000)

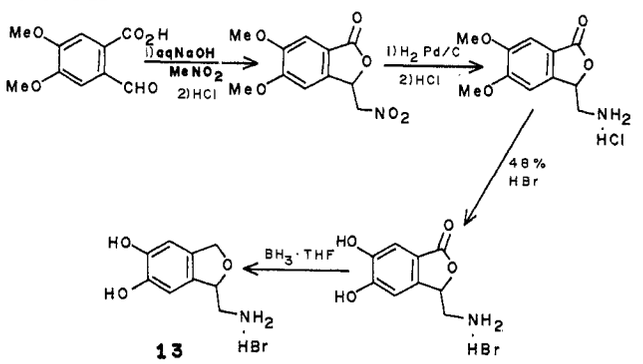
[a] Values given are nanomolar K_i values; see Experimental Section for radioligand and tissue used. [b] Compounds 14–18 were previously reported; see ref 1. [c] Ninety percent confidence limits shown in parentheses; see ref 12.

pared by reaction with nitromethane under aqueous alkaline conditions as previously reported for the dimethoxy derivative,[10] followed by acidic workup. Catalytic reduction of **2** over a 20% palladium-on-carbon catalyst in methanolic hydrochloric acid resulted in the acid addition salt of 1-(aminomethyl)-4,5-(methylenedioxy)phthalide (**3**). Compound **3** was then heated to reflux with borane in tetrahydrofuran (THF) followed by heating with methanolic HCl to give **4**.

Cleavage of the methylenedioxy moiety was readily accomplished by using BBr_3 in excess followed by quenching with methanol and removal of the boron as the trimethylborate/methanol azeotrope, to yield the catecholamine hydrobromide **5**. These boron tribromide cleavage reactions were done under inert atmosphere in methylene chloride at −78 °C to produce a clean conversion to the catechol.

Catalytic reductive alkylation of **3** using formaldehyde followed by BH_3·THF reduction provided the *N,N*-dimethyl compound **6** whereas reductive alkylation with propionaldehyde followed by borane reduction gave the [(*N,N*-di-*n*-propylamino)methyl]phthalan (**7**). It was found that the nitro group reduction and the reductive alkylation could be combined by performing the nitro group reduction in the presence of the appropriate aldehyde. Compounds **6** and **7** underwent BBr_3 cleavage of the methylenedioxy group to the respective catechols **8** and **9**. Reductive alkylation of **3**, first in the presence of benzaldehyde and then with formalin, gave after BH_3·THF reduction the dialkylated amine **10**. Amine **10** was catalytically debenzylated to give **11**, and BBr_3 cleavage of the methylenedioxy group afforded catechol **12**.

Scheme II



The corresponding 5,6-dihydroxy(aminomethyl)phthalan derivative **13** was prepared in a similar manner as shown in Scheme II with *m*-opianic acid as starting material.[11] In addition, cleavage of the dimethyl ethers was done with 48% HBr prior to borane reduction of the phthalide derivative since we found this to be a much cleaner preparative method. The compounds prepared for this study are shown in Table I.

Results and Discussion

The purpose of this investigation was to compare the α-adrenergic effects resulting from incorporation of an oxygen atom into position 2 of the 6-ERBCOP indan derivatives. We wanted to determine if the phthalan derivatives, because of the ability of the newly introduced oxygen atom to accept a hydrogen bond, would show improved α-receptor affinity and possibly α_1-/α_2-receptor

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(11) Bhattacharjee, D.; Popp, F. D. *J. Pharm. Sci.* **1980**, *69*, 120.

Table III. α_2 Selectivity of the Phthalan Derivatives[a] Expressed as the Ratio of the α_1 to α_2 Radioligand Binding Constant

compd[a]	K_i α_1/K_i α_2[a,b]
5 [**14**]	127 (83–196) [145 (96–221)]
8 [**15**]	109 (63–187) [276 (155–476)]
9 [**16**]	15 (9–28) [16 (8–31)]
12 [**17**]	112 (70–179) [323 (181–575)]
13 [**18**]	9.7 (3.3–28) [50 (22–114)]

[a] Indan derivatives shown in brackets. [b] Ninety percent confidence limits shown in parentheses.

selectivity relative to their 6-ERBCOP carbon isosteres, and to compare the phthalans to the ERBCOPs in terms of in vitro α-adrenergic activity.

The results from radioligand binding experiments are shown in Table II for the phthalan derivatives as well as their corresponding indan counterparts. As can be seen, the phthalan derivatives exhibited binding to both the α_1- and α_2-receptor, and in each case the binding to the α_2-receptor was better (lower K_i) than to the α_1-receptor.

The indan compounds showed greater α_2 selectivity (measured as the ratio of α_1 K_i to α_2 K_i; see Table III) than did the phthalan derivatives. The indans also possessed better affinity for the α_2-receptor relative to their phthalan counterparts except for **8** (Table II). In order to investigate whether the results from radioligand binding data would be expressed in assays of in vitro functional activity, we tested the newly described phthalans as well as the 6-ERBCOP indans in the isolated rabbit aorta[15] (α_1, Table IV) and the phenoxybenzamine-pretreated dog saphenous vein[16] (PBZ-DSV) (α_2, Table V).

In terms of α_1-receptor interaction, all of the compounds in Table IV were full agonists. The compounds containing the oxygen atom (i.e., the phthalans **5**, **8**, **12**) were as potent or slightly more potent than the corresponding carbon analogues (i.e., the indans **14**, **15**, **17**). Likewise, at the α_2-receptor all of the compounds in Table V were full agonists. However, in contrast to the results obtained from the rabbit aorta (α_1), the indans (**14**, **15**, **17**) were, in general, more potent than the phthalans (**5**, **8**, **12**) in the PBZ-DSV (α_2) in vitro assay. The exception was the *N,N*-dimethylphthalan derivative **8** which had also shown better α_2-radioligand binding affinity than the corresponding indan compound **15** (Table II). As was found for the radioligand binding affinities, the phthalans and the indans were selective for the α_2-receptor in these functional assays (Table VI). Also of interest was the potency of the indan **17**, being 30 times more potent than the NE in the PBZ-DSV (α_2) assay.

As can be seen from the radioligand binding data (Tables II and III), the phthalan compounds (**5**, **8**, **9**, **12**, and **13**) had α-adrenergic affinities similar to those of the corresponding 6-ERBCOP indan compounds after which they were modeled (**14**–**18**). Both types of compounds showed selectivity for the α_2-receptor in these radioligand binding assays; unlike the 6-ERBCOP derivatives, the 2-ERBCOP phthalan **13** like its 2-ERBCOP indan counterpart **18** showed relatively poor affinity for the α-adrenergic receptors and was virtually inactive. The α_2-binding of the *N,N*-di-*n*-propyl compounds **9** and **16** was relatively weak compared to that of the other 6-ERBCOP type compounds that had a nitrogen substituent no larger than methyl, thus accounting for the decrease in α_2 selectivity of these dipropyl derivatives.

The remaining 6-ERBCOP phthalans (**5**, **8**, and **12**) and indans (**14**, **15**, and **17**) demonstrated both strong α_2-adrenergic binding affinity as well as good α_2-receptor selectivity on the basis of radioligand binding. When these phthalans were compared to their indan analogues, it was seen that the relative α_2-receptor binding was somewhat diminished for phthalans **5** and **12**, but in the case of phthalan **8** the affinity for both the α_2- and particularly the α_1-receptors was improved relative to the corresponding indan **15** (Table II). The net effect was a decreased α_2 selectivity for these phthalans relative to the indan compounds (Table III).

When the in vitro effects of phthalans **5**, **8** and **12** and indans **14**, **15**, and **17** were examined (Tables IV–VI), a pattern similar to that found in the radioligand binding assay was found. Both the phthalans and the indans demonstrated a full agonistic response, and in all cases the index of the compounds (the ratio of the ED_{50} NE to the ED_{50} CPD) was better in the α_2 assay than in the α_1 assay, indicating a greater potency at α_2-receptors. As was found in the radioligand binding assay, the phthalans **5** and **12** showed decreased potency in the α_2 in vitro assay relative to their corresponding indan analogues **14** and **17** (Table V). Also paralleling the radioligand results was the profile of phthalan **8** relative to the 6-ERBCOP indan **15**. Compound **8** was somewhat more potent than **15** in the α_2 tissue, but the increase in α_1 activity of **8** relative to **15** was even greater. The overall pattern of in vitro activity demonstrated a decrease in the α_2 selectivity of the phthalans relative to their carbon analogues (Table VI).

We believe that these results are important for several reasons. First, the activity of the phthalan compounds was in accord with the ERBCOP hypothesis[1] in that the 6-ERBCOP phthalans **5**, **8**, and **12** showed potent α_1- and α_2-adrenergic agonism just as was seen for the 6-ERBCOP indans, whereas the 2-ERBCOP phthalan **13** like its 2-ERBCOP indan analogue **18** was virtually inactive toward α-adrenergic receptors.

Second, when the α_2 activity of the 6-ERBCOP phthalans was compared with the corresponding α_2 activity of the indan compounds, we found that in some cases (**5** vs. **14** and **12** vs. **17**) the indans were more potent, while in another case (**8** vs. **15**) the phthalan was more potent. We believe that no real benefit to the α_2 activity results from the introduction of an oxygen atom into the carbocyclic ring. This coupled with the potent α_2 agonism demonstrated by the 6-ERBCOP indans (in particular, **17**) leads us to conclude that contrary to the results previously reported on conformationally mobile phenethylamines[5] a NE type β-hydroxyl group is not an absolute requirement for

(12) Because radioligand-binding data is log normally distributed[13] we have reported geometric mean values of the K_i along with the 90% confidence limits (CL) for each value. To report such data as an arithmetic mean (AM) plus or minus the standard error of the AM is inappropriate since it does not give a true representation of the variance of the data. Furthermore, if one wishes to examine differences in the data, it is important to recall that the usual tests for the statistical significance of such differences[14] assume that a normal distribution exists for the data under consideration, and it would not be valid to apply such tests to the *AM* of *log normally* distributed data.

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Table IV. Indices and ED_{50} Values for Compounds Tested in Vitro in the Rabbit Aorta (α_1)

compd	index[a] (ED_{50} NE/ED_{50} CPD)	n	E_{max}[a,b]	ED_{50} NE ($\times 10^7$)[c]	ED_{50} CPD ($\times 10^7$)[c]
5	0.04 ± 0.01	4	107 ± 4	1.52 (0.5–4.7)	38.5 (10.7–140)
8	1.0 ± 0.07	2	114 ± 3	1.24 (1.06–1.44)	1.19 (0.91–1.55)
12	0.32 ± 0.02	4	126 ± 4	0.84 (0.45–1.53)	2.60 (2.09–3.23)
14	0.017 ± 0.003	2	102 ± 11	1.92 (0.008–480)	115 (1.50–8940)
15	0.27 ± 0.05	4	105 ± 11	1.21 (0.65–2.26)	4.13 (2.56–6.66)
17	0.27 ± 0.1	4	109 ± 4	1.05 (0.49–2.24)	4.98 (4.31–5.74)

[a] Mean of n experiments ± SEM. [b] Expressed as a percent of the maximum response of the tissue to NE. [c] Geometric mean with 90% confidence limits in parentheses; see ref 13.

Table V. Indices and ED_{50} Values for Compounds Tested in Vitro in the PBZ-Pretreated Dog Saphenous Vein (α_2)

compd	index[a] ED_{50} NE/ED_{50} CPD	n	E_{max}[a,b]	ED_{50} NE ($\times 10^7$)[c]	ED_{50} CPD ($\times 10^7$)[c]
5	1.45 ± 0.13	2	90 ± 1	4.38 (2.35–8.19)	3.04 (0.93–9.87)
8	4.00 ± 0.56	4	107 ± 3	6.99 (4.72–10.37)	1.80 (0.92–3.52)
12	1.69 ± 0.16	2	94 ± 0.1	5.40 (1.71–17.07)	3.21 (0.57–18.25)
14	3.55 ± 0.95	5	91 ± 2	5.72 (3.49–9.37)	1.99 (1.10–3.60)
15	2.05 ± 0.35	5	101 ± 3	8.86 (7.24–10.86)	4.66 (3.48–6.24)
17	29.6 ± 8.5	4	81 ± 2	3.66 (2.63–5.07)	0.14 (0.08–0.24)

[a–c] See footnotes to Table IV.

Table VI. α_2 Selectivity for Compounds in the in Vitro Assays (Index α_2/Index α_1) and Radioligand Binding Assays (K_i α_1/K_i α_2)

compd	in vitro[a] α_2 selectivity: index α_2/index α_1	radioligand binding[b] α_2 selectivity: K_i α_1/K_i α_2
5	36.3 ± 9.6	127
8	4.0 ± 0.6	109
12	5.3 ± 0.6	112
14	209 ± 67	145
15	7.6 ± 1.9	276
17	110 ± 52	323

[a] Ratio of the mean index values ± probable error calculated from the SEMs of the index values. [b] See Table III for 90% confidence limits.

affinity to or stimulation of the α_2-adrenoceptor of all phenethylamines. Rather, potent α_2-adrenergic activity and selectivity can be obtained provided that the correct conformation for activity is built into the sympathomimetic agent. This is quite evident from **17**, which is much more potent than NE at the α_2-receptor while maintaining a respectable α_2/α_1 selectivity ratio (Table VI). Interestingly, the 6-ERBCOP indans (particularly **17**) raise the question as to whether or not these agents indeed adhere to the Easson–Stedman hypothesis[17] in terms of their α_2-receptor interaction.

It would appear that these 6-ERBCOP indans bind to the α_2-receptor via a two-point attachment as was suggested by Patil[3] for (+)- and (−)-α-methyldopamine and related compounds. These conformationally restricted phenethylamines (6-ERBCOPs) do not therefore require a β-hydroxyl or equivalent for α_2-receptor interaction as evidenced from both their potency as well as selectivity.

If indeed for all phenethylamines the basic nitrogen atom, a benzylic hydroxyl group (i.e., β-hydroxyl), and the phenyl ring (with m- and p-hydroxyl groups) bind to α_2-adrenergic receptors via a three-point attachment as others[5] have suggested, then **17** lacks one "essential" point, the β-hydroxyl. However, **17** as noted previously, is nearly 30 times more potent than NE at the α_2-receptor in the PBZ-DSV. The incorporation of an oxygen atom into the molecule (i.e., **12**) which could mimic the β-hydroxyl did not improve the potency at the α_2-receptor. Rather, **12** showed α_2-receptor potency only slightly greater than NE in the PBZ-DSV (Table V). Possibly, the phthalan oxygen atom is positioned in an incorrect orientation for α_2-receptor interaction (although we outlined above why we think it is in the correct position), or the H atom (which the phthalan compounds lack) of the NE β-hydroxyl group interacts with the α_2-adrenoceptor. However, the 6-ERBCOP phthalans (**5**, **8**, **12**) are all equipotent to, or more potent than, (−)-NE unlike, for example, dopamine or (+)-NE, shown[5] to be less active in various preparations.

Last, in contrast to the α_2 results, the α_1 activity of the phthalans was equal to (**12** vs. **17**) or better than (**5** vs. **14** and **8** vs. **15**) that of the corresponding indans (Table IV). Also the α_2 selectivity (Table VI) of the phthalans was less than that of their indan analogues. As a result, we feel that the oxygen atom of these phthalans (and that of the NE β-hydroxyl group) may play a role in binding to the α_1-adrenergic receptor.

In conclusion, insertion of an oxygen atom at position 2 of the 6-ERBCOP indan derivatives resulted in compounds that possessed slightly greater α_1-receptor potency but no general trend in α_2-receptor potency. The oxygen isosteres, however, like the corresponding 6-ERBCOP indan derivatives are selective for the α_2-receptor relative to the α_1-receptor on the basis of both radioligand-binding assays and in vitro assays. Like the 6-ERBCOP indan derivatives, the 6-ERBCOP phthalans exhibit strong radioligand-binding affinities as well as potent in vitro α-adrenergic agonism. We conclude that while the NE type β-hydroxyl group may be beneficial for binding to the α_1-adrenoceptor, it is not an absolute requirement for binding to or stimulation of the α_2-adrenergic receptor, provided the correct conformation for activity is built into the phenethylamine type sympathomimetic agent.

Experimental Section

α_1 Activities Using Isolated Rabbit Aorta. Female rabbits, weighing 2–5 kg, were sacrificed by cervical dislocation. The thoracic cavity was immediately opened and the descending aorta was removed and placed in a petri dish containing Krebs buffer aerated with 95% O_2 and 5% CO_2. The Krebs buffer solution was prepared as follows (mM concentrations): NaCl 119, $NaHCO_3$ 25, KCl 4.7, $MgSO_4$ 1.5, KH_2PO_4, 1.2, $CaCl_2$ 2.5, glucose 11, NaEDTA 0.03, and ascorbic acid 0.3. The buffer was prepared daily from a concentrated stock solution and was adjusted to a pH of 7.4.

A helical strip of aorta was mounted in a 10-mL tissue bath containing Krebs buffer and was attached to a force transducer (Grass or Statham) so that an initial tension of 2 g was applied.

(17) Easson, L. H.; Stedman, E. *Biochem. J.* **1933**, *27*, 1257.

The tissue was allowed to equilibrate for 1 h during which time the tissue was washed four times and the tension reset to 2 g until it had stabilized. A mixture of 95% O_2 and 5% CO_2 was continuously bubbled through the tissue bath and reservoir. Stirring in the bath was provided by vigorous bubbling of the gas mixture. The temperature of the tissue bath was maintained at 37 ± 0.5 °C by means of a constant-temperature bath that circulated approximately 8 L/min of warmed water through the water jacket of the tissue bath. Standard weights were hung on the force transducers to calibrate them. Contractions, measured by the force transducers, were recorded on a Grass Model 7 polygraph, and periodic samples of the data were acquired by an on-line computer system that included a PDP 11/45 and DEC 10 computer.

A cumulative dose–response curve of contraction was produced with the standard agonist, NE, from 1×10^{-8} to 1×10^{-3} M doses. Drugs were administered by means of an adjustable microliter pipet in volumes usually from 10 to 100 μL. The response to each dose of standard or test compound was allowed to plateau before the administration of the next dose. Following a dose–response series, the tissue was washed with aliquots of buffer every 10–15 min for 60–90 min until the tension returned to base line or reached a plateau near the base-line level. The tension of the tissues was readjusted until it stabilized at 2 g before the next dose–response series.

α_2 Activities Using PBZ-Pretreated Dog Saphenous Vein. Rings (3–4-mm wide) of lateral saphenous veins excised from beagle dogs of either sex were suspended in 10-mL tissue baths containing bicarbonate buffer of the following mM composition: NaCl 119, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.5, KH_2PO_4 1.2, $NaHCO_3$ 20, dextrose 11, ascorbic acid 0.3, NaEDTA 0.03, cocaine 0.03, hydrocortisone hemisuccinate 0.04, and propranolol 0.004. The solution was gassed with 95% O_2 and 5% CO_2 at 37 °C, pH 7.45. Isometric contractions of the tissues, preloaded with a tension of 2 g, were measured with Grass FT03 strain gauges and recorded on a Grass Model 7 polygraph.

Following an equilibration period of 15–20 min and maximal contraction by NE (1×10^{-4} M), the tissues were washed for 60 min after which they were exposed to phenoxybenzamine (PBZ) (1×10^{-7} M) for 30 min. At the end of the PBZ treatment a thorough washout followed for 60 min. Tissues were then adjusted to 2 g tension, and a control cumulative dose–response curve was obtained for the standard agonist, NE. After washout of NE (45–60 min), tissues were again equilibrated and a cumulative dose–response curve of the tested agonist was obtained.

Radioligand-Binding Assays. Tissue Preparation. Twenty male Sprague–Dawley rats weighing 250–350 g were anesthetized with sodium pentobarbital (50 mg/kg, ip), and the brains and livers were quickly removed and placed in assay buffer (Tris·HCl, 50 mM, pH 7.7 at 25 °C) at 4 °C. Cerebral cortices were separated from the remainder of the brains, and tissues were pooled prior to homogenization. The organs were weighed, and pooled tissues were separately homogenized in 20 volumes of preparation buffer (Tris·HCl, 50 mM, pH 7.7 at 25 °C, containing 5 mM EDTA), with a Tekmar SDT homogenizer at full speed for two 10-s bursts. The homogenates were centrifuged at 50000*g* (4 °C) for 10 min, and the supernatant was discarded. The pellets were resuspended by homogenization as above in 20 volumes of preparation buffer and recentrifuged for 10 min, and the supernatant was again discarded. The final pellet was resuspended in 6.25 volumes of assay buffer, flash frozen in liquid nitrogen, and stored at −70 °C until the day of the experiment. Tissues were thawed at room temperature and thereafter maintained at 4 °C.

Assay Methods. All assays were performed in a light-subdued laboratory, with a total incubation volume of 1.0 mL. Four hundred and fifty microliters of radioligand (either [^{3}H]prazosin [sp act. 23 Ci/mmol, Amersham, Arlington Heights, IL] for α_1 assays[18] or [^{3}H]rauwolscine[19] [sp act. 79 Ci/mmol, New England Nuclear, Boston, MA] for α_2 assays) in assay buffer was incorporated with 50 μL of 0.3 mM ascorbic acid, containing phentolamine (10^{-5} M, nonspecific binding), varying concentrations of test compounds, or no addition (total binding). Incubation commenced upon the addition of 500 μL of membrane homogenate in assay buffer, resulting in a final protein concentration of 50–150 μg/mL, determined by the method of Bradford.[20]

Equilibrium binding was evaluated after a 50-min incubation at 25 °C for α_1 assays or a 2-h incubation period at 4 °C for α_2 assays. Receptor-bound radioligand was separated from free ligand by filtration under −180 mmHg vacuum through Whatman 934AH filters, which were dried in a hot-air oven at 60 °C. Three milliliters of Ready-Solv NA (Beckman) was added, and the solubilized ligand was counted to a 4.5% 2σ error level in a Beckman LS3800 liquid scintillation counter at approximately 63% counting efficiency. The "added" radioligand tubes were not filtered, but 0.1 mL was dried on a filter, combined with 3 mL of Ready-Solv, and counted. Quenching was determined by the H# method.

In saturation binding experiments, eight concentrations of radioligand between 10^{-11} and 10^{-8} were utilized. Total (buffer control) and nonspecific (10^{-5} M phentolamine) binding were determined in triplicate at each concentration of radioligand. The radioligand affinity (K_D) and apparent receptor density (B_{max}) were evaluated by using the method of Scatchard.[21] Total and nonspecific binding data were also analyzed via the SCAFIT program of Munson and Rodbard,[22] to determine if the data could be best described by either a one- or two-site model.

In the competition binding assays, total and nonspecific binding were each determined with five replicates. Specific binding was the arithmetic difference between total binding and nonspecific binding. Affinities of each of the tested compounds were evaluated by measuring the percent inhibition of specific binding, with use of at least four concentrations between 10^{-10} and 10^{-3} M, with duplicate determinations at each concentration. The concentration at which 50% inhibition of specific binding was observed and the pseudo-Hill coefficient were calculated from the linear relationship between logit percent specific bound (log [%{1 − %}]) vs. log concentration. The dissociation constant (K_i) was derived according to the equation of Cheng and Prusoff:[23]

$$K_i = IC_{50}/(1 + [L]/K_D)$$

The ligand concentration [L] used in this calculation was the arithmetic difference between the total ligand added to each incubation tube as determined from the counts in the "added" tubes and the radioligand bound at the IC_{50} concentration. The ligand affinity for the receptors (K_D) was held constant for each radioligand.

Chemistry. Proton magnetic resonance (^{1}H NMR) spectra were recorded on a Varian T-60, a Varian XL-100, or a General Electric QE-300 instrument using either Me_4Si or DDS as internal standard. Melting points were determined on a Thomas-Hoover Unimelt and are uncorrected. Elemental analyses were done in-house, and determined values are within ±0.4% of theoretical values. Solvents were reagent grade and were used without additional purification unless otherwise indicated.

General Procedure for the Synthesis of (Aminomethyl)phthalides. 1-(Aminomethyl)-4,5-(methylenedioxy)phthalide Hydrochloride (3). A mixture of 9.4 g (40 mmol) 4,5-(methylenedioxy)-1-(nitromethyl)phthalide, 225 mL of CH_3OH, 50 mL of H_2O, 3.4 mL (41 mmol) of concentrated HCl, and 1.0 g of 20% palladium on carbon was hydrogenated at 3 atm in a Parr shaker for 14 h at 50 °C. After filtration and evaporation of the solvents, the solid was crystallized from alcohol, affording 9.0 g (93%) of **3**: mp 295–296 °C; IR (KBr) 3440, 3020, 2900, 1760, 1500, 1480, 1265 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.17 (dd, 1, J = 8, 14 Hz), 3.70 (dd, 1, J = 3, 14 Hz), 5.87 (dd, 1, J = 3, 8 Hz), 6.33 (s, 2), 7.20 (d, 1, J = 8 Hz), 7.40 (d, 1, J = 8 Hz); mass spectrum, m/e (relative abundance) 207 (M^+, 20), 178 (100), 149 (50), 122 (65). Anal. ($C_{10}H_{10}ClNO_4$) C, H, N.

General Procedure for the Synthesis of (Aminomethyl)phthalans. 1-(Aminomethyl)-4,5-(methylenedi-

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(23) Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.

oxy)phthalan Hydrochloride (4). A mixture of 12 g (49 mmol) of **3**, 50 mL of THF, and 150 mL (150 mmol) of 1 M borane THF (BH_3·THF) was heated at reflux for 8 h. After cooling, the reaction was quenched with methanolic HCl. The resulting solid was filtered, slurried with 2-propanol, and refiltered to give 10.2 g (90%) of **4**: mp 169–170 °C; IR (KBr) 3000, 2900, 1470, 1250 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.80–3.30 (m, 4), 5.10 (br s, 2), 5.30–5.53 (m, 1), 6.10 (s, 2), 6.97 (s, 2), 10.10 (br s, 3, absent with D_2O); mass spectrum, *m/e* (relative intensity) 193 (M^+, 4), 163 (100), 135 (15), 77 (35).

General Procedure for Cleavage of the Methylenedioxy Group. 1-(Aminomethyl)-4,5-dihydroxyphthalan Hydrobromide (5). To a mixture of 1.4 g (6.1 mmol) of **4** and 50 mL of CH_2Cl_2 under nitrogen at −78 °C was added dropwise a solution of 2.22 mL (23.4 mmol) of BBr_3 in 10 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 3 h and then quenched at −78 °C by dropwise addition of 25 mL of CH_3OH followed by stirring at room temperature for 2 h. Evaporation afforded a solid, which was recrystallized from methanol/ether to give 0.9 g (56%) of **5**: mp 218–220 °C; IR (KBr) 3220, 1615, 1515, 1240, 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.50–3.50 (m, 2), 5.00 (br s, 2), 5.17–5.50 (m, 1), 6.00 (d, 1, *J* = 8 Hz), 6.87 (d, 1, *J* = 8 Hz), 7.30–8.60 (m, 3, absent with D_2O); mass spectrum, *m/e* (relative intensity) 181 (M^+, 1), 151 (15), 30 (100). Anal. ($C_9H_{12}BrNO_3$) C, H, N.

1-[(*N*,*N*-Dimethylamino)methyl]-4,5-(methylenedioxy)-phthalan Hydrochloride (6). Reduction of the corresponding phthalide (4.5 g, 19.3 mmol) with BH_3·THF by the general method above gave 1.8 g (36%) of **6**: mp 220–221 °C; ^1H NMR (Me_2SO-d_6) δ 2.81 (s, 6), 3.19 (dd, 1, *J* = 8, 14 Hz), 3.65 (br d, 1, *J* = 14 Hz), 5.03 (br s, 2), 5.67 (br d, 1, *J* = 8 Hz), 6.07 (s, 2), 6.93 (s, 2), 11.33 (br s, 1, absent with D_2O); mass spectrum, *m/e* 221 (M^+), 163, 135, 105, 77, 58. Anal. ($C_{12}H_{16}ClNO_3$) C, H, N.

1-[(*N*,*N*-Di-*n*-propylamino)methyl]-4,5-(methylenedioxy)phthalan Hydrochloride (7). Reduction of the corresponding phthalide (7.0 g, 21.4 mmol) with 1 M BH_3·THF (155 mL, 155 mmol) by the general method gave 2.9 g (43%) of **7**: mp 170–172 °C; IR (KBr) 3500, 2920, 1470, 1245, 1040 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.80 (t, 6, *J* = 8 Hz), 1.30–2.00 (m, 4), 2.80–3.50 (m, 6), 5.07 (br s, 2), 5.80 (br d, 1, *J* = 8 Hz), 6.10 (s, 2), 6.96 (s, 2), 12.80 (br s, 1, absent with D_2O). Anal. ($C_{16}H_{24}ClNO_3$) C, H, N.

4,5-Dihydroxy-1-[(*N*,*N*-dimethylamino)methyl]phthalan Hydrobromide (8). Cleavage of 1.9 g (7.4 mmol) of the methylenedioxy derivative **6** by the general method above gave 1.1 g (51%) of **8**: mp 190–192 °C; IR (KBr) 3200, 1510, 1385 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.80 (s, 6), 3.17 (dd, 1, *J* = 9, 14 Hz), 3.50 (br d, 1, *J* = 14 Hz), 5.00 (br s, 2), 5.50 (br d, 1, *J* = 9 Hz), 6.60 (d, 1, *J* = 8 Hz), 6.80 (d, 1, *J* = 8 Hz), 11.40 (br s, 1, absent with D_2O). Anal. ($C_{11}H_{16}BrNO_3$) C, H, N.

4,5-Dihydroxy-1-[(*N*,*N*-di-*n*-propylamino)methyl]-phthalan Hydrobromide (9). Cleavage of 2.5 g (8 mmol) of **7** by the general method gave 1.2 g (43%) of **9**: mp 105–107 °C; IR (KBr) 3300, 2970, 1510, 1285 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.90 (t, 6, *J* = 8 Hz), 1.33–2.17 (m, 4), 3.00–3.60 (m, 6), 5.10 (br s, 2), 5.70 (br d, 1, *J* = 7 Hz), 6.77 (d, 1, *J* = 8 Hz), 6.93 (d, 1, *J* = 8 Hz), 11.40 (br s, 1, absent with D_2O). Anal. ($C_{15}H_{24}BrNO_3 \cdot {}^1/_2H_2O$) C, H, N.

4,5-(Methylenedioxy)-1-[(*N*-methylamino)methyl]-phthalan Hydrochloride (11). Reduction of 1-[(*N*-benzyl-*N*-methylamino)methyl]-4,5-(methylenedioxy)phthalide (11.4 g, 36.6 mmol) with 265 mL (265 mmol) of 1 M BH_3·THF by the general method described above gave 5.67 g (46%) of 1-[(*N*-benzyl-*N*-methylamino)methyl]-4,5-(methylenedioxy)phthalan hydrochloride (**10**): mp 213–214 °C; mass spectrum, *m/e* 297 (M^+). Hydrogenation of 5.67 g (17 mmol) of **10** in a Parr shaker with 250 mL of CH_3OH and 0.57 g of 20% palladium on carbon was done at room temperature under 3 atm of hydrogen for 2 h. The resulting mixture was filtered and the filtrate evaporated to dryness. Recrystallization from CH_3OH gave 2.14 g (52%) of **11**: mp 244–245 °C; IR (KBr) 3420, 2940, 1465, 1245, 1030 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.57 (s, 3), 3.05 (dd, 1, *J* = 9, 13 Hz), 3.38 (dd, 1, *J* = 2.5, 13 Hz), 5.03 (d, 1, *J* = 12 Hz), 5.12 (dd, 1, *J* = 2.5, 12 Hz), 5.44 (br d, 1, *J* = 9 Hz), 6.07 (s, 2), 6.86 (d, 1, *J* = 8 Hz), 6.93 (d, 1, *J* = 8 Hz), 9.0 (br s, 2, absent with D_2O); mass spectrum, *m/e* (relative intensity) 207 (M^+, 3), 163 (35), 44 (100). Anal. ($C_{11}H_{14}ClNO_3$) H, N; C: calcd, 54.21; found, 53.73.

4,5-Dihydroxy-1-[(*N*-methylamino)methyl]phthalan Hydrobromide (12). Cleavage of 1.5 g (6.2 mmol) of **11** by the general method afforded 0.8 g (47%) of **12**: mp 221–222 °C; IR (KBr) 3200, 2970, 1510, 1265, 1025 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.60 (s, 3), 3.05 (dd, 1, *J* = 8.5, 13 Hz), 3.38 (dd, 1, *J* = 2, 13 Hz), 4.96 (d, 1, *J* = 13 Hz), 5.07 (dd, 1, *J* = 2.5, 13 Hz), 5.35 (br d, 1, *J* = 8.5 Hz), 6.01 (d, 1, *J* = 8 Hz), 6.77 (d, 1, *J* = 8 Hz), 8.60 (br s, 1, absent with D_2O), 8.90 (br s, 1, absent with D_2O), 9.27 (br s, 1, absent with D_2O); mass spectrum, *m/e* (relative intensity) 195 (M^+, 5), 151 (60), 44 (100). Anal. ($C_{10}H_{14}BrNO_3$) C, H, N.

1-(Aminomethyl)-5,6-dihydroxyphthalide Hydrobromide. 1-(Aminomethyl)-5,6-dimethoxyphthalide hydrochloride (4.5 g, 17.3 mmol) was heated under reflux with 100 mL of 48% HBr for 4.5 h and then allowed to cool to room temperature overnight. The HBr was removed under vacuum, and the residue was washed with a small volume of H_2O. The solid was filtered to give 2.1 g (41%) of 1-(aminomethyl)-5,6-dihydroxyphthalide hydrobromide: mp 292–294 °C dec; IR (KBr) 3400, 2900, 1750, 1600, 1510, 1360 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.70–4.00 (m, 2), 5.77 (br d, 1, *J* = 7 Hz), 7.20 (s, 1), 7.27 (s, 1), 8.35 (br s, 3, absent with D_2O). Anal. ($C_9H_{10}BrNO_4 \cdot H_2O$) C, H, N.

1-(Aminomethyl)-5,6-dihydroxyphthalan Hydrobromide (13). Reduction of 3.5 g (12.7 mmol) of 1-(aminomethyl)-5,6-dihydroxyphthalide hydrobromide was accomplished as described in the general method with 94.6 mL (94.6 mmol) of 1 M BH_3·THF to give 1.8 g (54%) of **13**: mp 237–238 °C dec; IR (KBr) 3200, 1610, 1520, 1355, 1320 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.97 (dd, 1, *J* = 8, 14 Hz), 3.30 (dd, 1, *J* = 14 Hz), 4.97 (br s, 2), 5.30 (br s, 1), 6.80 (s, 2), 7.70–9.10 (br m, 5, absent with D_2O); mass spectrum, *m/e* 181 (M^+). Anal. ($C_9H_{12}BrNO_3$) H, N; C: calcd, 41.24; found, 40.83.

Acknowledgment. We thank Robert Warner, Steven Buckner, Patricia Morse, Josef Cerny, Dusanka Stanisic, John Cain, and Karen Oheim for technical assistance, Dr. Arthur Hancock for helpful discussions, and Cyndy Davis and Joan Doerrer for typing this manuscript.

Registry No. **2**, 104834-85-7; **3**, 96142-99-3; **4**, 96142-82-4; **5**, 96142-86-8; **5** (free base), 104834-92-6; **6**, 96163-06-3; **6** (phthalide), 104834-89-1; **7**, 96142-84-6; **7** (phthalide), 104834-90-4; **8**, 96142-88-0; **8** (free base), 104834-93-7; **9**, 96142-89-1; **9** (free base), 104848-70-6; **10**, 104834-86-8; **10** (phthalide), 104834-91-5; **11**, 104834-87-9; **12**, 104834-88-0; **12** (free base), 104834-94-8; **13**, 96142-92-6; **13** (free base), 104834-95-9; 4-carboxy-5-formylbenzodioxole, 58343-48-9; formaldehyde, 50-00-0; propionaldehyde, 123-38-6; benzaldehyde, 100-52-7; *m*-opianic acid, 490-63-1; nitromethane, 75-52-5; 1-(nitromethyl)-5,6-dimethoxyphthalide, 103989-27-1; 1-(aminomethyl)-5,6-dimethoxyphthalide hydrochloride, 103797-23-5; 1-(aminomethyl)-5,6-dihydroxyphthalide hydrobromide, 78219-03-1.