Esters of *N*-*tert*-Butylarterenol. Long-Acting New Bronchodilators with Reduced Cardiac Effects

Benjamin F. Tullar, Hiroaki Minatoya, and Roman R. Lorenz*

Departments of Chemistry and Pharmacology, Sterling-Winthrop Research Institute, Rensselaer, New York 12144.
Received September 10, 1975

The preparation of various esters of *N*-*tert*-butylarterenol is described. Esterification of the phenolic OH groups has increased bioavailability, prolonged bronchodilation, and reduced tachycardia. The substitution of aromatic esters compared with simple aliphatic esters improved markedly these pharmacological properties. Of a number of esters tested, compound **45** (bitolterol) demonstrated the most favorable pharmacological properties as a bronchodilator. Its long duration of action and significant bronchodilator–cardiovascular separation are briefly described.

In their metabolic studies of *dl*-isoproterenol-7-^3H in the dog, Conway et al.[1] have observed that the orally administered drug was inactivated largely by conversion to conjugates of glucuronic and sulfuric acids during absorption. These observations have suggested to us that esterification of the vulnerable phenolic OH groups of isoproterenol as well as some other catecholamines might reduce inactivation and prolong activity. The synthesis and biological testing of various esters were initiated in 1966.[2,3]

In 1947 Bretschneider[4] made the 3,4-diacetate and 3,4-dipropionate esters of isoproterenol and other catecholamines, but no reports of pharmacological studies have appeared. Zolss[5] prepared a series of bisesters of α-alkylaminomethyl-3,4-dihydroxybenzyl alcohols as well as the diacetates of a few catecholamines. Only preliminary pharmacologic results were reported and these indicated that the esters were quantitatively similar to the parent compounds, but with weaker activity and more prolonged effects. He also reported an improvement in the ratio of bronchodilator activity to heart rate stimulation with the esters.

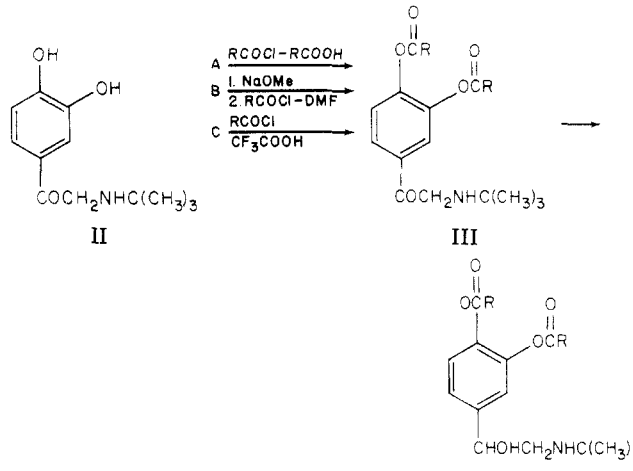
Initially, several esters of isoproterenol were prepared and tested in this laboratory. These esters showed improved bioavailability and duration of activity over the parent compound (unpublished observations). However, since *N*-*tert*-butylarterenol was known to be about twice as potent as a bronchodilator and one-half as active in causing cardiac stimulation as isoproterenol (unpublished observations), a number of 4-monoesters and 3,4-diesters of this compound were synthesized and tested.

In this report, we describe the syntheses and pharmacologic properties of these esters. A preliminary report of the ester that possesses the most favorable properties as a bronchodilator, namely bitolterol **45** (di-*p*-toluate ester of *N*-*tert*-butylarterenol), has been presented by Minatoya and Tullar.[6] The oral and aerosol forms of this compound are now being evaluated clinically and early results are favorable.

Chemistry. The esters of I were all prepared by reduction of esters of 1-*tert*-butylamino-3',4'-dihydroxyacetophenone,[7] II, either catalytically or with sodium borohydride in methanol. In many cases the HCl salts of the esters of I could not be obtained in crystalline form but usually the methanesulfonates were nicely crystalline salts. This was especially true with salts of aromatic esters. A very useful solvent for crystallization of these salts was isopropyl acetate (Table I).

The intermediate esters III were prepared by Bretschneider's[4] acid–acid chloride procedure in the case of many of the aliphatic esters. For more hindered aliphatic and for aromatic acids reaction of the acid chloride with the disodium salt of II in DMF was a useful procedure. However, better yields were generally obtained when the HCl salt of II was treated in trifluoroacetic acid solution with an excess of the acid chloride (Table II).

4-Monoesters[8] were frequently found as by-products in these esterifications and became the principal product when only 1 equiv of acid chloride was used. Repetition of the acylation procedure on a monoester with a different acid chloride produced mixed esters such as the 4-anisoate 3-benzoate, etc.

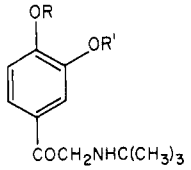


Biological Results in Dogs. The esters of *N*-*tert*-butylarterenol were tested for their bronchodilator and cardiovascular activities and compared with their parent compound and isoproterenol. Results of these observations are summarized in Table III.

1. Monoesters (Compounds 27–32). Compared with the parent compound I which possessed a potent but short duration of bronchodilator action (<2 h), this series of compounds showed a moderate degree of activity with a longer duration of action lasting about 2 h. Their onset of action was rapid (within 4 min). The heart rate effect of several of these esters (**27**, **28**, and **30**) was considerably less than that of compound I or isoproterenol, indicating that esterifying the 4-OH moiety had altered, in some degree, the biological properties of the catecholamines.

2. Diesters (Compounds 33–49). With a few exceptions, moderate to marked bronchodilator activity was seen with the majority of compounds in this diester series. They were active by various routes of administration and, intravenously, the duration of action of compounds **39**, **40**, **42**, and **45** was longer (>4 h) than that of the monoesters. The onset of action occurred within 5–10 min but the maximal effect was generally seen 30 min after administration. Intraduodenally, compounds **39** and **45** showed a longer duration of bronchodilator action (approximately 5 h) than compound I. By aerosol compounds **42**, **44**, and **45** were longer acting (>4 h) than the parent compound (<2 h).

Table I. Esters of 1-*tert*-Butylaminomethyl-3',4'-dihydroxyacetophenone



Compd no.	R	R'	Salt	Mp, °C	Yield, %	Method	Formula
1	$(CH_3)_3CCO$-	H-	HCl	268-270 dec	52	D	$C_{17}H_{25}NO_4 \cdot HCl$
2	$(CH_3)_2CHCH_2CO$-	H-	CH_3SO_3H	242-245 dec	41	D	$C_{17}H_{25}NO_4 \cdot CH_4O_3S$
3	$(CH_3)_3CCH_2CO$-	H-	CH_3SO_3H	240-245 dec	61	E	$C_{18}H_{27}NO_4 \cdot CH_4O_3S$
4	4-$CH_3C_6H_4CO$-	H-	CH_3SO_3H	265 dec	68	D	$C_{20}H_{23}NO_4 \cdot CH_4O_3S$
5	3-$CH_3C_6H_4CO$-	H-	CH_3SO_3H	265-268 dec	48	D	$C_{20}H_{23}NO_4 \cdot CH_4O_3S$
6	4-$CH_3OC_6H_4CO$-	H-	HCl	235 dec	71	D	$C_{20}H_{23}NO_5 \cdot HCl$
7	$CH_3(CH_2)_2CO$-	$CH_3(CH_2)_2CO$-	HCl	212-215 dec	79	A	$C_{20}H_{29}NO_5 \cdot HCl$
8	$(CH_3)_2CHCO$-	$(CH_3)_2CHCO$-	HCl	221-223 dec	20	B	$C_{20}H_{29}NO_5 \cdot HCl$
9	$(CH_3)_2CHCH_2CO$-	$(CH_3)_2CHCH_2CO$-	HCl	220-222 dec	81	A	$C_{22}H_{33}NO_5 \cdot HCl$
10	$CH_3CH_2CH(CH_3)CO$-	$CH_3CH_2CH(CH_3)CO$-	HCl	218-221 dec	66	A	$C_{22}H_{33}NO_5 \cdot HCl$
11	$(CH_3)_3CCO$-	$(CH_3)_3CCO$-	HCl	243 dec	28	B	$C_{22}H_{33}NO_5 \cdot HCl$
12	c-$C_3H_4CH_3CO$-	c-$C_3H_4CH_3CO$-	HCl	253-255 dec	81	A	$C_{22}H_{31}NO_5 \cdot HCl$
13	$(CH_3)_3CCH_2CO$-	$(CH_3)_3CCH_2CO$-	HCl	225 dec	16	B	$C_{24}H_{37}NO_5 \cdot HCl$
14	$C_6H_{11}CO$-	$C_6H_{11}CO$-	HCl	204-210 dec	21	B	$C_{26}H_{37}NO_5 \cdot HCl$
15	$CH_3(CH_2)_2C(CH_3)_2$-CO-	$CH_3(CH_2)_2C(CH_3)_2$-CO-	HCl	183-185 dec	35	B	$C_{28}H_{41}NO_4 \cdot HCl$
16	C_6H_5CO-	C_6H_5CO-	HCl	215-218 dec	23	B	$C_{26}H_{25}NO_5 \cdot HCl$
17	2-$CH_3C_6H_4CO$-	2-$CH_3C_6H_4CO$-	CH_3SO_3H	134-137 dec	56	C	$C_{28}H_{29}NO_5 \cdot CH_4O_3S$
18	3-$CH_3C_6H_4CO$-	3-$CH_3C_6H_4CO$-	HCl	215-218 dec	68	C	$C_{28}H_{29}NO_5 \cdot HCl$
19	4-$CH_3C_6H_4CO$-	4-$CH_3C_6H_4CO$-	HCl	217-220 dec	80	C	$C_{28}H_{29}NO_5 \cdot HCl$
20	3,5-$(CH_3)_2C_6H_3CO$-	3,5-$(CH_3)_2C_6H_3CO$-	CH_3SO_3H	126-128 dec	64	C	$C_{30}H_{33}NO_5 \cdot CH_4O_3S$
21	4-$CH_3OC_6H_4CO$-	4-$CH_3OC_6H_4CO$-	HCl	205-208 dec	25	B	$C_{28}H_{29}NO_7 \cdot HCl$
22	4-$CH_3C_6H_4CH_2CO$-	4-$CH_3C_6H_4CH_2CO$-	HCl	205-208 dec	65	C	$C_{30}H_{33}NO_5 \cdot HCl$
23	4-$CH_3OC_6H_4CH_2CO$-	4-$CH_3OC_6H_4CH_2CO$-	HCl	204-207 dec	50	C	$C_{30}H_{33}NO_7 \cdot HCl$
24	4-$CH_3C_6H_4CO$-	CH_3CO-	CH_3SO_3H	204-207 dec	91[a]	A	$C_{22}H_{25}NO_5 \cdot CH_4O_3S$
25	4-$CH_3C_6H_4CO$-	C_6H_5CO-	CH_3SO_3H	170-172 dec	57[a]	F	$C_{27}H_{27}NO_5 \cdot CH_4O_3S$
26	4-$CH_3OC_6H_4CO$-	CH_3CO-	CH_3SO_3H	150-152 dec	90[a]	A	$C_{22}H_{25}NO_6 \cdot CH_4O_3S$

[a] Refers to the introduction of the second acyl group (R').

Among the aliphatic diesters, the compounds with shorter carbon chains (**33** and **34**) had a shorter duration of action than those with longer carbon chains. Presence of a tertiary carbon in the acid portion (**34**) increased the duration of action. The substitution of aromatic rings, in general, increased the duration of bronchodilator activity without affecting its potency. Of these, compound **45** (bitolterol) demonstrated the most favorable pharmacological properties as a bronchodilator. It was active by various routes of administration and the estimated intraduodenal intravenous activity ratio (the ratio of doses, id/iv, producing comparable maximum bronchodilation estimated from the dose–response data) of compound **45** was 2 compared with the ratio of 200 for the parent compound and 800 for isoproterenol. These values indicated that the intraduodenal bioavailability or absorption efficiency of **45** was approximately 100 times greater than that of the parent compound I and 400 times that of isoproterenol II.

Further improvement accomplished with compound **45** was in its significant separation of cardiostimulatory and bronchodilator effects. Compared with its parent compound and isoproterenol at an equiactive bronchodilator dose level, ED_{60} (the dose that produces 60% bronchodilation), compound **45** had only $^1/_8$th the chronotropic effect of the parent compound and $^1/_{13}$th that of isoproterenol. The blood pressure was hardly affected by compound **45**.

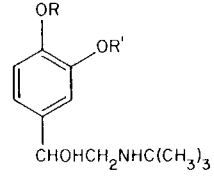
3. Mixed Esters (Compounds 50–52). With the exception of compound **52**, the duration of bronchodilator action of these esters was relatively short (<1–2 h). The bronchodilator and heart rate activities of the mixed esters were markedly increased when one of the substitutions was a shorter aliphatic acid (**50**). These properties, however, were again altered by having an acetyl group at position 3 and an aromatic (4-$CH_3OC_6H_4CO$) anisoyl group at position 4 of the ring (**52**). Compound **52** showed marked activity having a rapid onset and long duration of action particularly on aerosol (intratracheal) administration.

In both enzymatic (plasma) and nonenzymatic studies of the hydrolysis rates of various esters of *N-tert*-butylarterenol, Levitt et al. (unpublished observations) found that aliphatic diesters with less than four carbons and the monoesters, in general, were rapidly hydrolyzed, whereas aromatic diesters were more slowly hydrolyzed. The hydrolysis rates observed in vitro were fairly well correlated with the bronchodilator activity (onset, degree, and duration) observed in the intact, anesthetized dog study. The prolonged bronchodilator effect as well as greater bronchodilator–cardiovascular separation of compound **45** was due to greater concentration of the ester in lung tissues and to slow hydrolysis of this ester releasing gradually the active catecholamine.[9] The complete pharmacological activity of bitolterol (**45**) in comparison with that of its parent compound and isoproterenol will be published in an appropriate pharmacological journal.

Experimental Section

Acylation. Diesters. Method A. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 3',4'-Bis(3,3-dimethylbutyrate) Hydrochloride (14). A mixture of 80 g of II·HCl in 300 ml of *t*-BuCOOH and 125 g of *t*-BuCOCl was stirred and heated slowly to 106° with increasing rate of HCl evolution. The suspension was maintained at this temperature until the starting material went into solution (about 10 min); then the temperature was raised to 104° and kept at that point until cessation of gas evolution.

Table II. Esters of 1-(*tert*-Butylaminomethyl)-3′,4′-dihydroxybenzyl Alcohol



Compd no.	R	R′	Salt	Mp, °C	Yield, %	Method	Formula	Analyses
27	$(CH_3)_3CCO$–	H–	CH_3SO_3H	175–177	65	A	$C_{17}H_{27}NO_4 \cdot CH_4O_3S$	C, H, S
28	$(CH_3)_2CHCH_2CO$–	H–	CH_3SO_3H	148–150	62	A	$C_{17}H_{27}NO_4 \cdot CH_4O_3S$	N, S
29	$(CH_3)_3CCH_2CO$–	H–	CH_3SO_3H	176–178	81	A	$C_{18}H_{29}NO_4 \cdot CH_4O_3S$	N, S
30	4-$CH_3C_6H_4CO$–	H–	CH_3SO_3H	203–205	62	A	$C_{20}H_{25}NO_4 \cdot CH_4O_3S$	C, H, S
31	3-$CH_3C_6H_4CO$–	H–	CH_3SO_3H	165–168	61	A	$C_{20}H_{25}NO_4 \cdot CH_4O_3S$	C, H, S
32	4-$CH_3OC_6H_4CO$–	H–	HCl	211–213	76	A	$C_{20}H_{25}NO_5 \cdot HCl$	C, H, Cl, N
33	$CH_3(CH_2)_2CO$–	$CH_3(CH_2)_2CO$–	HCl	136–138	75	A	$C_{20}H_{31}NO_5 \cdot HCl$	C, H, Cl, N
34	$(CH_3)_2CHCO$–	$(CH_3)_2CHCO$–	HCl	190–191	62	A	$C_{20}H_{31}NO_5 \cdot HCl$	C, H, N
35	$(CH_3)_2CHCH_2CO$–	$(CH_3)_2CHCH_2CO$–	HCl	171–173	81	A	$C_{22}H_{35}NO_5 \cdot HCl$	C, H, Cl, N
36	$CH_3CH_2CH(CH_3)CO$–	$CH_3CH_2CH(CH_3)CO$–	HCl	163–165	85	A	$C_{22}H_{35}NO_5 \cdot HCl$	C, H, Cl
37	$(CH_3)_3CCO$–	$(CH_3)_3CCO$–	HCl	248–249	78	A	$C_{22}H_{35}NO_5 \cdot HCl$	C, H, Cl
38	c-$C_3H_4CH_3CO$–	c-$C_3H_4CH_3CO$–	HCl	210–212	70	A	$C_{22}H_{31}NO_5 \cdot HCl$	C, H, Cl
39	$(CH_3)_3CCH_2CO$–	$(CH_3)_3CCH_2CO$–	HCl	226–228	85	A	$C_{24}H_{39}NO_5 \cdot HCl$	C, H, Cl
40	$C_6H_{11}CO$–	$C_6H_{11}CO$–	HCl	212–213	77	A	$C_{26}H_{39}NO_5 \cdot HCl$	C, H, Cl
41	$CH_3CH_2CH_2C(CH_3)_2CO$–	$CH_3CH_2CH_2C(CH_3)_2CO$–	CH_3SO_3H	107–109	68	A	$C_{26}H_{43}NO_5 \cdot CH_4O_3S$	C, H, S
42	C_6H_5CO–	C_6H_5CO–	HCl	214–216	61	A	$C_{26}H_{27}NO_5 \cdot HCl$	C, H, Cl
43	2-$CH_3C_6H_4CO$–	2-$CH_3C_6H_4CO$–	CH_3SO_3H	151–153	83	A	$C_{28}H_{31}NO_5 \cdot CH_4O_3S$	C, H, S
44	3-$CH_3C_6H_4CO$–	3-$CH_3C_6H_4CO$–	CH_3SO_3H	135–137	68	A	$C_{28}H_{31}NO_5 \cdot CH_4O_3S$	C, H, S
45	4-$CH_3C_6H_4CO$–	4-$CH_3C_6H_4CO$–	CH_3SO_3H	170–172	91	B	$C_{28}H_{31}NO_5 \cdot CH_4O_3S$	C, H, N, S
46	3,5-$(CH_3)_2C_6H_3CO$–	3,5-$(CH_3)_2C_6H_3CO$–	CH_3SO_3H	190–193	88	A	$C_{30}H_{35}NO_5 \cdot CH_4O_3S$	C, H, N, S
47	4-$CH_3OC_6H_4CO$–	4-$CH_3OC_6H_4CO$–	HCl	165–166	63	A	$C_{28}H_{31}NO_7 \cdot HCl$	C, H, Cl
48	4-$CH_3C_6H_4CH_2CO$–	4-$CH_3C_6H_4CH_2CO$–	HCl	115–117	81	A	$C_{30}H_{35}NO_5 \cdot HCl$	C, H, Cl, N
49	4-$CH_3OC_6H_4CH_2CO$–	4-$CH_3OC_6H_4CH_2CO$–	HCl	124–127	68	A	$C_{30}H_{35}NO_7 \cdot HCl$	C, H, Cl, N
50	4-$CH_3C_6H_4CO$–	CH_3CO–	CH_3SO_3H	171–173	71	A	$C_{22}H_{27}NO_5 \cdot CH_4O_3S$	C, H, N, S
51	4-$CH_3C_6H_4CO$–	C_6H_5CO–	CH_3SO_3H	183–185	65	A	$C_{27}H_{29}NO_5 \cdot CH_4O_3S$	C, H, N, S
52	4-$CH_3OC_6H_4CO$–	CH_3CO–	CH_3SO_3H	172–174	70	A	$C_{22}H_{27}NO_6 \cdot CH_4O_3S$	C, H, N, S

Table III. Biological Results in Dogs

Compd no.	Route[a]	Dose range, μg/kg	Biological activities: Bronchodilation[b] Deg[c]	Bronchodilation Duration, h	Heart rate Deg[d]	Heart rate Duration, h
27	Iv	10-20	++	<2	++	<0.5
28	Iv	5-20	++	<2	++	<1
29	Iv	5	++	>3	e	e
30	Iv	5-10	++	>3	++	<0.5
	It	440-880	++	<2		
31	Iv	50-100	+++	<2	++	<0.5
	It	440-880	+++	<2		
32	It	400-800	++	<2	+	<0.5
33	Iv	4-8	+++	<2	+	<1
	Id	200-400	+++	>3		
	It	380	+++	<2		
34	Iv	5	+	<0.5		
35	Iv	4-8	+++	<2	+	<1
	Id	200-400	++	3	++	<3
	It	400-800	+++	<2		
36	Iv	5-10	++	<1		
37	Iv	20-100	+++	3	+	<2
	Id	50-100	+++	3		
	It	400-800	++	<2		
38	Iv	5	++	<1		
	Id	50	++	2		
39	Iv	200	+++	>4	+	<1
	Id	100-200	++	<5		
	It	430-860	+	<3		
40	Iv	100-200	++	<5	+	<3
41	Iv	5-10	++	<1		
42	Iv	30-60	++	<4	++	
	It	2000-2700	+++	4	+	1
43	Iv	100-200	+	<4	+	<0.5
	It	300-1200	+	<3		
44	Iv	140-280	+++	>3		
	Id	140	++	2		
	It	300-1200	++	<4		
45	Iv	35-140	+++	>5	+	2
	Id	70-280	+++	>5	+	2
	It	540-1080	++	>5	±	<1
46	It	590-1180	+	<3		
47	Iv	25-100	+	1	+	<2
	Id	50-100	+	<3		
48	It	530-1060	++	2		
49	Iv	25-100	+++	2		
50	Iv	25-50	+++	<1	++	<0.5
	It	520-1040	+++	>1	±	<1
51	Iv	25-50	+++	2		
	It	520-1040	++	2		
52	Iv	20-40	+++	>4	+	2
	Id	160	+++	>5	+	<3
	It	250-1000	+++	>6	±	<1
I (*N*-*t*-B)	Iv	0.35-2	+++	>1	++	<0.25
	Id	50-300	++	3	++	3
	It	150-300	+++	<2	+	1
Isoproterenol	Iv	0.3-2	+++	<1	+++	<0.25
	Id	50-240	+	<2	++	2
	It	125-250	+++	<1	+	1

[a] Routes of administration: iv = intravenous, id = intraduodenal, it = intratracheal (by aerosol). [b] Expressed as percent inhibition of bronchoconstriction induced by either carbachol (2-4 μg/kg iv) or histamine (20-50 μg/kg iv). Approximately 40% of the tests on each compound was done by histamine. Since the results with either agent were comparable, they were combined and averaged (see ref 11). [c] Degree of bronchodilation: the average values of no less than three dogs per dose. + = 20-45%, ++ = 45-70%, +++ = >70%. These represent the responses from the higher dose. [d] Increase in heart rate (beats/min): ± = 5-15, + = 20-40, ++ = 40-60, +++ = >60 (n = >4/dose). [e] Where there are no symbols, the data are not yet available.

About 200 ml of solvent was removed in vacuo, and the crystalline residue was slurried in 400 ml of ether, filtered, and recrystallized from 1 l. of boiling 2-propanol to give 130 g of pure 14, mp 225-228° dec.

Method B. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 3',4'-Diisovalerate Dihydrochloride (9). Under nitrogen 26 g (0.1 mol) of II·HCl was dissolved in 200 ml of DMF and treated with stirring at 25° with 17 g (0.3 mol) of NaOMe to give a dark red solution. About 50 ml of DMF was distilled off in vacuo to remove liberated MeOH and any moisture present.

Isovaleryl chloride (24 g, 0.2 mol) was dripped in at 10°. After stirring 2 h at 25°, the DMF was distilled off in vacuo. The dark red color disappeared rapidly during this period. The residue was dissolved by stirring with a mixture of 200 ml of H_2O and 200 ml of Et_2O. The Et_2O layer was washed with diluted NaOH and then with H_2O. After drying and removal of the Et_2O, the residue in *i*-PrOH was acidified with HCl. The diester HCl crystallized and 18.1 g (42%) was obtained, mp 222-228° dec.

Acidification of the alkaline wash with AcOH yielded 8.2 g of the 4-monoester acetate salt. This in 300 ml of EtOH was treated

with 3.4 ml of 68% CH_3SO_3H solution to precipitate 6.0 g of **2**, mp 242–245°.

Method C. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 3',4'-Di-*p*-toluate Hydrochloride (19). To a suspension of 100 g of II·HCl in 250 ml of CF_3COOH was added 17.5 ml of *p*-toluoyl chloride over a period of 15 min with vigorous evolution of HCl. The mixture was heated slowly to 80° and held at that temperature for 1 h. The volatile portion was distilled in vacuo and the residue was stirred in Et_2O and filtered to give a nearly quantitative yield of the diester trifluoroacetate salt. This salt was partitioned between Et_2O and H_2O and basified with NaOH solution. The Et_2O layer was treated with a solution of 40 ml of concentrated HCl in 200 ml of water. The crystalline product which precipitated from this two-phase system was filtered and dried to yield 165 g (86%) of **19**, mp 215–217°.

Acylation. Monoesters. Method D. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 4-*p*-Toluate Methanesulfonate (4). Under nitrogen 17 g (0.3 mol) of NaOMe was added rapidly to a stirred solution of 26 g (0.1 mol) of II·HCl in 200 ml of DMF at room temperature. After removing 50 ml of distillate in vacuo, 16 g (0.104 mol) of *p*-toluoyl chloride was dripped in at 10° over a period of 30 min. The mixture was stirred for 1 h allowing the temperature to rise to 25°. After removing the solvent under vacuum the residue was treated with Et_2O and dilute NaOH solution. The aqueous layer was separated and acidified with AcOH to yield the 4-(*p*-toluate) ester acetate salt which was collected and washed with H_2O and then Et_2O. This acetate salt was dried and then suspended in 300 ml of DMF and treated with 14 g of 68% CH_3SO_3H to give rapid solution and then almost immediate precipitation of the methanesulfonate. The salt was filtered, washed with acetone, and dried at 60% in vacuo to yield 30 g (68%) of pure **4**, mp 265° dec. (When only 2 equiv of NaOMe were used, the yield of the monoester was 23%.)

Method E. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 4-(3,3-Dimethylbutyrate) Methanesulfonate (3). While stirring at room temperature 8 ml of 3,3-dimethylbutyryl chloride was added dropwise to a solution of 13 g of II·HCl (0.05 mol) in 35 ml of CF_3COOH. Stirring was continued for 30 min until a clear solution resulted and the evolution of HCl ceased. The acid was distilled off in vacuo, the residue was slurried in Et_2O, and filtered. This trifluoroacetate salt was slurried in 400 ml of *i*-PrOAc and basified by addition of 8 ml of concentrated NH_4OH in 50 ml of H_2O. The organic layer was separated, washed with H_2O, and then acidified with 3.5 g of 68% CH_3SO_3H. The precipitate was collected and washed with *i*-PrOAc and Et_2O. After recrystallization from 200 ml of 95% EtOH a 13.0-g crop of **3**, mp 245° dec, resulted.

Mixed Esters. Method F. 3',4'-Dihydroxy-2-(*tert*-butylamino)acetophenone 3-Acetate 4-*p*-Toluate Methanesulfonate (24). A mixture of 20 g of **4**·CH_3SO_3H in 200 ml of AcOH and 100 ml of AcCl was stirred and heated at reflux to a clear solution for 1.5 h. The solvents were removed under vacuum and the residue was crystallized from *i*-PrOAc to yield 20 g (91%) of **24**, mp 204–207°.

Reduction. Method A. α-(*tert*-Butylaminomethyl)-3',4'-dihydroxybenzyl Alcohol 3',4'-Bis(3,5-dimethylbenzoate) Methanesulfonate (46). A solution of 28 g (0.048 mol) of **20** in 200 ml of DMF was shaken in the presence of 3 g of 10% Pd/C under 50 lb of H_2 pressure until the calculated amount of H_2 had reacted (about 1.5 h).

After removal of the catalyst and then the solvent by vacuum evaporation, the residue was crystallized from 300 ml of boiling *i*-PrOAc. The product after drying at 70° in vacuo weighed 25.0 g (89%), mp 190–193°.

Method B. α-(*tert*-Butylaminomethyl)-3',4'-dihydroxybenzyl Alcohol 3',4'-Di-*p*-toluate Methanesulfonate (45). A cold solution of 5.4 g of $NaBH_4$ in 25 ml of MeOH was added to a mixture of 100 g of **19** in 500 ml of MeOH over a period of 1 h while the temperature of the reaction was kept below 5°. Most of the solvent was evaporated in vacuo and the residue was treated with 350 ml of *i*-PrOAc. The mixture was stirred rapidly while a solution of 260 ml of 10% $NaHCO_3$ in H_2O was added slowly. The organic layer was separated and dried over $CaSO_4$. The solution was acidified with 17 ml of 98% CH_3SO_3H. The solution was partially concentrated in vacuo during which time the product precipitated. After cooling, the product was filtered and dried at 60° in vacuo to give 85.5 g (85%) of **45**, mp 170–172°.

Pharmacology. Bronchodilator activity of these compounds was tested in the intact, anesthetized (pentobarbital Na, 30 mg/kg iv), open-chest dog maintained under artificial respiration using a constant volume Harvard respirator attached to a tracheal cannula. A specially designed, nonrebreathing leucite valve was attached to the cannula regulating the in- and outflows of air. Bronchoconstriction was induced by the intravenous injections of carbachol (2–4 μg/kg) or histamine diphosphate (20–50 μg/kg) and the changes in airway pressure were measured by a Statham pressure transducer (P23B) and recorded on a Grass (Model 17) polygraph as reported by Minatoya and Spilker.[10] Each compound was tested with both carbachol and histamine using different animals to differentiate an antihistaminic effect from an isoproterenol-like effect.[11] Bronchodilation was expressed as percent inhibition of the control carbachol or histamine-induced bronchoconstriction.

Heart rate was studied in anesthetized, spontaneously respiring dogs. Heart rate was monitored by an EKG (Sanborn) with lead II attachment and blood pressure was measured by a Statham pressure transducer (P23A) from the right femoral artery and recorded on the polygraph.

Stock solutions of the drugs were prepared fresh in distilled water and the dilutions were made in physiological saline and were kept on ice. Test solutions (<1 ml volume) were administered intravenously into the right femoral vein. During inspiration aerosols were delivered directly into the trachea through an actuator attached to a cannula. The aerosols were generated from pressurized solutions discharged through metered valves which delivered 50 μl of product (100–400 μg) per valve actuation. A test solution (1.5 ml) was injected into the duodenal lumen with a 24-gauge needle. The duodenum had been prepared accessible through a small midline incision in the abdomen.

Acknowledgment. The authors express their appreciation to Dr. W. D. Conway for his early participation in the consideration of the ester compounds. We extend our thanks to Dr. E. Bogado, Ms. M. Gosztyla, Ms. K. Spada, and Ms. J. Tyll for their able assistance in carrying out the biological tests. Aerosol preparations were kindly supplied by Dr. W. G. Gorman and his staff.

References and Notes

(1) W. D. Conway, H. Minatoya, A. M. Lands, and J. M. Shekosky, *J. Pharm. Sci.*, **57**, 1135 (1968).
(2) H. Minatoya, B. F. Tullar, and W. D. Conway (Sterling Drug Inc.), Belgian Patent 748178 (1970).
(3) H. Minatoya, B. F. Tullar, and W. D. Conway, *Chem. Abstr.*, **74**, 53268c (1971).
(4) H. Bretschneider, *Monatsh. Chem.*, **77**, 385 (1947).
(5) G. Zolss, *Sci. Pharm.*, **32**, 76 (1964).
(6) H. Minatoya and B. F. Tullar, *Pharmacologist*, **16**, 211 (1974).
(7) J. R. Corrigan, M. Langermann, and M. L. Moore, *J. Am. Chem. Soc.*, **71**, 530 (1949).
(8) The 4 position of the monoesters was assigned by NMR spectral evidence. Also previous workers, Mukki and Honkanen [*Acta Chem. Scand.*, **13**, 320 (1959)], reported that benzoylation of 3,4-dihydroxyacetophenone under similar conditions gave the 4-benzoate ester.
(9) L. D. Shargel and S. A. Dorrbecker, *Drug Metab. Dispos.*, in press.
(10) H. Minatoya and B. A. Spilker, *Br. J. Pharmacol.*, **53**, 333 (1975).
(11) B. A. Spilker and H. Minatoya, *Arch. Int. Pharmacodyn. Ther.*, **217**, 201 (1975).