whereas **1a** was active at 0.1 mg/kg. In the rat, estrogenicity of **1d** was only approximately 0.04% that of **1a**. In the normal rat hypocholesterolemic assay **1d** was inactive at 10 mg/kg, whereas **1a** at 0.02 mg/kg produced cholesterol depression of 50–60%. Although at 10 mg/kg compound **1d** was not hypocholesterolemic, it did produce marginal lowering of the weights of the testes, ventral prostate, and the seminal vesicles.

Compound **2d** was not contraceptive in mice (50 mg/kg) and was only weakly uterotropic in mice. In rats, its estrogenicity was likewise very weak in comparison with **2a**. A dose of 250 μg/rat of **2d** increased the uterine weight in immature rats to the same level as 0.2 μg/rat of **2a**. However, a tenfold increase in dosage of **2d** produced only a small additional increment in uterine weight, whereas 2 μg of **2a** resulted in a uterine weight nearly twice that produced by 0.2 μg of **2a**. Compound **2d** had hypocholesterolemic activity at 50 mg/kg (−60%) and at the same dose reduced the weights of sexual end points. As with **1d**, **2d** at 10 mg/kg produced nonsignificant lowering of serum cholesterol but gave a marginal depression of sexual end points. Compound **5e** was inactive in all of the above-mentioned assays.

Thus, substitution of the 5-tetrazoyl group for carboxyl in the potent estrogenic acids **1a** and **2a** resulted in nearly complete loss of biological activity in all of the assays described. The lack of activity may result from failure of the tetrazole group to bind to estrogenic receptors, failure of the tetrazole derivatives to reach receptor sites, or inability of the tetrazoles to undergo metabolic conversion to biologically active forms analogous to those required for **1a**[8] and **2a**.[9]

Experimental Section

Melting points are capillary and are uncorrected. All compounds had ir and nmr spectra consistent with assigned structures. Where elemental analyses are indicated by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

3-Ethyl-2-methyl-4-phenyl-Δ⁴-cyclohexenecarboxamide (1b). A 3.40-g sample of the acid **1a** (mp 157–161°, reported[6] 158–163°) was treated with $SOCl_2$ in CH_2Cl_2 to produce the acid chloride.§ The crude acid chloride was stirred with cold concd NH_4OH to yield the amide **1b**: 3.15 g (93%); mp 144–150° (MeCN). *Anal.* ($C_{16}H_{21}NO$) C, H, N.

5-(3-Ethyl-2-methyl-4-phenyl-Δ⁴-cyclohexenyl)tetrazole (1d). Triethylamine (2.07 g, 0.02 mole) was added to a soln of the amide **1b** (2.45 g, 0.01 mole) in $POCl_3$ (15 ml), and the soln was heated under reflux for 1.75 hr. Excess $POCl_3$ was removed at 15 mm. A $CHCl_3$ soln of the residue was washed with H_2O and aqueous NH_4OH. Evapn of the dried $CHCl_3$ soln left the nitrile **1c** as an oil (2.06 g, 91%). The crude nitrile (2.02 g, 0.009 mole) in DMF (20 ml) contg NaN_3 (0.62 g, 0.01 mole) and NH_4Cl (0.51 g, 0.01 mole) was heated at 118° for 18 hr. The DMF was removed under reduced pressure, and the residue was partitioned between aqueous 1 *N* NaOH and Et_2O. The aqueous basic layer was acidified and extd with fresh Et_2O. Evapn of the dried Et_2O soln yielded **1d** (0.57 g, 24%); recrystd (aqueous EtOH) to a hydrated cryst form of **1d**, mp 105–120°. The analytical sample was dried at 100° (0.1 mm) over P_2O_5 to a glass. *Anal.* ($C_{16}H_{20}N_4$) C, H, N.

3-(6-Methoxy-2-naphthyl)-2,2-dimethylvaleramide (2b). A commercial sample‡ of the acid **2a** was converted to the amide **2b** by the procedure described for **1b**: yield, 75%; mp 144–145.5° (MeCN). *Anal.* ($C_{18}H_{23}NO_2$) C, H, N.

3-(6-Methoxy-2-naphthyl)-2,2-dimethylvaleronitrile (2c) was prepd from the amide **2b** (3.00 g) using the procedure described for **1c**: yield of **2c**, 2.45 g (87%); mp 111–113° (EtOH). *Anal.* ($C_{18}H_{21}NO$) C, H, N.

5-[2-(6-Methoxy-2-naphthyl)-1,1-dimethylbutyl]tetrazole (2d). A mixt of $AlCl_3$ (5.70 g, 0.043 mole) and NaN_3 (8.25 g, 0.127 mole) in diglyme (73 ml) was warmed to 75°, and then a soln of the nitrile **2c** (8.15 g, 0.031 mole) in diglyme (37 ml) was added. The mixt was stirred under reflux for 16 hr. Most of the solvent was removed at reduced pressure, and the residue was acidified with 6 *N* aqueous HCl. An ether ext of the product was washed with aqueous 1 *N* NaOH. Acidification of the basic extracts yielded **2d** (1.81 g, 19%): mp 168–170°. Recrystn (aqueous EtOH) gave mp 171–173°. *Anal.* ($C_{18}H_{22}N_4$) C, H, N.

3-(6-Methoxy-2-naphthyl)valeric Acid (5b). 6-Methoxy-2-propionaphthone[10] and ethyl bromoacetate were condensed according to a general procedure[11] to yield the hydroxyester **3** (67%): mp 72.5–73.5° (*i*-PrOH). *Anal.* ($C_{18}H_{22}O_4$) C, H.

Dehydration of **3** by heating under reflux in AcOH contg *p*-TsOH gave a mixt of the ene esters **4a**:**4b** in approximately a 2:3 ratio (nmr): bp 161–165° (0.1 mm) (82% yield). *Anal.* ($C_{18}H_{20}O_3$) C, H.

Hydrogenation of **4** in abs EtOH contg 5% Pd/C gave **5a** (90%): bp 143–146° (0.04 mm). *Anal.* ($C_{18}H_{22}O_3$) C, H.

Hydrolysis of the ester **5a** (23.32 g) by heating under reflux for 18 hr in 80% EtOH (120 ml) contg KOH (6.13 g) yielded, after acidification, the acid **5b** (20.52 g, 97%): mp 92–94.5° (aqueous EtOH). *Anal.* ($C_{16}H_{18}O_3$) C, H.

5-[2-(6-Methoxy-2-naphthyl)butyl]tetrazole (5e). Following the general procedure described above, the acid **5b** was converted to the amide **5c** (89%): mp 112.5–113.5° (toluene). *Anal.* ($C_{16}H_{19}NO_2$) C, H, N. Dehydration of **5c** using the procedure described above gave the nitrile **5d** (84%): mp 58.5–61°. *Anal.* ($C_{16}H_{17}NO$) C, H, N.

The nitrile **5d** was treated with NaN_3–NH_4Cl as described in the procedure for **1d** to produce the tetrazole **5e** (30%): mp 138–139.5° (MeCN). *Anal.* ($C_{16}H_{18}N_4O$) C, H, N.

Acknowledgment. We express our appreciation to Dr. J. E. MacNintch for the hypocholesterolemic data and to the analytical and spectroscopic departments of these laboratories for their services.

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§ An aliquot of the acid chloride was dissolved in MeOH. Vpc analysis of the resultant methyl ester indicated the same isomeric ratio as the starting acid **1a**.

Adamantyl Analogs of 2′-(3-Dimethylaminopropylthio)cinnamanilide†

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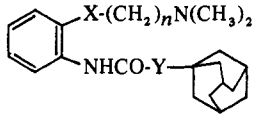
Several recent reports have described the synthesis and biological activity of a variety of adamantane derivatives.[1-10] This note describes the syntheses and immunosuppressive activity of representative adamantyl analogs (**2–9**) of 2′-(3-dimethylaminopropylthio)cinnamanilide [cinanserin (**1**)], which had been developed in our laboratories by Krapcho, *et al.*[11-14]

Chemistry. 1-Adamantanecarboxylic acid‡ (**10**), 1-ada-

† Cinanserin is the approved generic name for 2′-(3-dimethylaminopropylthio)cinnamilide (**1**).

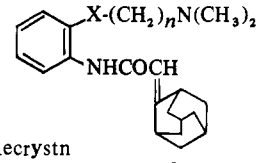
‡ Aldrich Chemical Co., Milwaukee, Wisconsin.

Table I

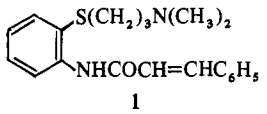


No.	X	n	Y	Recrystn solvent	Mp, °C	Formula	Analyses
2	S	3	CH=CH	MeCN-Et_2O	144-147	$C_{24}H_{34}N_2OS \cdot HCl \cdot 0.5H_2O$	C, H, N, S
3	O	3		EtOAc-Et_2O	221-223	$C_{22}H_{32}N_2O_2 \cdot HCl$	C, H, N
4	O	3	CH_2	C_6H_6-hexane	187-189	$C_{23}H_{34}N_2O_2 \cdot HCl$	C, H, N
5	O	3	CH=CH	MeOH-EtOAc	196-197	$C_{24}H_{34}N_2O_2 \cdot HCl$	C, H, N
6	CH_2	1		MeCN	230-231	$C_{21}H_{30}N_2O \cdot HCl$	C, H, N
7	CH_2	1	CH_2	MeCN-Et_2O	216-218	$C_{22}H_{32}N_2O \cdot HCl$	C, H, N

Table II



No.	X	n	Recrystn solvent	Mp, °C	Formula	Analyses
8	S	3	MeCN-Et_2O	130-132	$C_{23}H_{32}N_2OS \cdot HCl$	C, H, N, Cl
9	O	3	Me_2CO	207-210	$C_{23}H_{32}N_2O_2 \cdot HCl$	C, H, N



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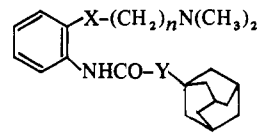
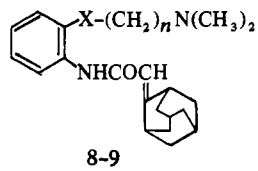
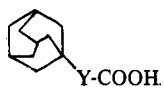


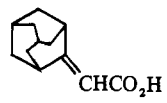
2-7



8-9



10, Y = ---
11, Y = CH_2
12, Y = CH=CH



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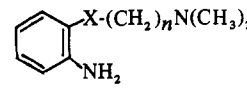

14

mantaneacetic acid‡ (**11**), 1-adamantaneacrylic acid[15] (**12**), and Δ^2,α-adamantaneacetic acid[15] (**13**) were converted to their acid chlorides and allowed to react with the properly substituted anilines[11-14] (**14**) to give the anilides listed in Tables I and II. Many of the compounds were obtained as hygroscopic hydrochloride salts.

Biological Data. The compounds synthesized were screened for immunosuppressive activity in the mouse-sheep red blood cell test.[14,16] The ratio of the concentration of antibodies in the sera of control mice to that in the sera of the drug-treated mice (antibody index) was determined. The results are given in Table III.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

The intermediate substituted amines were prepd as previously described.[11-14] The syntheses of compds listed in Tables I and II are illustrated by the following.

Table III

No.	Immunosuppressive act.[a]
1	5
2	2
3	1
4	1
5	3
6	2
7	2
8	3
9	0

[a] Drugs were given at a dose of 25 mg/kg (sc). In the case of cinanserin, it was necessary to make a 64-fold dilution of the control sera to match the hemagglutinin titre of the sera from the drug-treated mice. Activity ratings: dilution of 64 = 5, 32 = 4, 16 = 3, 8 = 2, 2 to 4 = 1 and 1 = 0. All the compounds tested were less active than cinanserin.

2'-{[3-(Dimethylamino)propyl]thio}-1-adamantaneacrylanilide Hydrochloride (2). A soln of 1.65 g (8 mmoles) of 1-adamantaneacrylic acid[15] in 75 ml of dry $CHCl_3$ was heated under gentle reflux with 10 ml of $SOCl_2$ for 0.5 hr. The excess of $SOCl_2$ was removed *in vacuo*, the last traces being stripped off by the addn of 10 ml of dry PhH. To the solid acid chloride obtained (dissolved in 50 ml of dry $CHCl_3$), a soln of 1.68 g (8 mmoles) of 2-(3-dimethylaminopropyl)thioaniline[11-14] in 25 ml of dry $CHCl_3$ was added dropwise at room temp. The mixt was then stirred at room temp for 1.5 hr. The solid obtained after the evapn of $CHCl_3$ was crystd twice from MeCN-Et_2O to give 2.8 g (80%) of **2** as cryst powder (hygroscopic), mp 144-147°. *Anal.* ($C_{24}H_{34}N_2OS \cdot HCl \cdot 0.5H_2O$) C, H, N, S.

Acknowledgment. The author is indebted to Dr. J. Bernstein for his advice and encouragement during the course of this investigation. The author wishes to thank Dr. R. C. Millonig and his associates for the biological data and Mr. J. Alcino and his associates for the microanalyses.

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Resolution of Terbutaline, a New β-Sympathomimetic Amine

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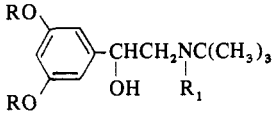
A recent article published in this Journal,[1] describing the resolution of salbutamol, prompts us to report an investigation[2] on the resolution of terbutaline, 1-(3',5'-dihydroxyphenyl)-2-(*tert*-butylamino)ethanol, where benzyl groups have been used for protection of the phenolic groups during the resolution.

The preparation[2] and pharmacological properties[3] of terbutaline have recently been described and it has been shown that this compound is a potent adrenergic β receptor stimulating agent, predominantly acting on the β_2 receptors.

Chemistry. Similar compounds, *e.g.*, orciprenaline,[4] have been resolved with unprotected phenolic groups, but owing to the unfavorable pK_a values of the hydroxyl groups and the ammonium group, it is difficult to extract the free base with an organic solvent in a good yield. Thus, after resolution of the racemic base, the salt with the optically active acid is dissolved in a suitable solvent and an optically inactive acid is added. The salt with this acid is then precipitated from the mixture with ether. The possibility of coprecipitation of the other salt makes this procedure less attractive. However, such problems can be completely eliminated as described below for terbutaline (**1**).



1, R = H; R_1 = H
2, R = $C_6H_5CH_2$; R_1 = $C_6H_5CH_2$

Compound **2** (racemic base) was treated with (−)-dibenzoyltartaric acid and formed a well-crystallized salt. After six recrystallizations to get reasonable optical purity, the salt was suspended in water, aqueous ammonia added, and the amine easily extracted with ether. A salt with a suitable optically inactive acid can then be prepared and isolated in the usual way. The protecting groups are then easily removed by catalytic hydrogenation to give one of the enantiomers of **1**. The salt of the other enantiomer can be prepared from the residual base from the mother liquors of the first resolution procedure. Two recrystallizations were found to give a reasonable optical purity.

Pharmacology. In 1966 and 1967, Lands, *et al.*,[5-7] showed, by means of rank order technique, that the adrenergic β receptors in the heart and the bronchi were not identical and classified them as β_1 and β_2 receptors. According to this theory, functions associated with β_1 stimulation are: myocardial excitation, relaxation of small intestine, and lipolysis in adipose tissue, whereas β_2 stimulation is associated with bronchodilatation, vasodilatation, and glycogenolysis. Since the racemate of terbutaline shows a very good selectivity for the β_2 receptors, investigation on the β-stimulating effect of each enantiomer on bronchi and heart muscle was carried out to see if a still better selectivity could be achieved in this way.

Table I. Biological Activity of the (−) and (+) Isomers of Terbutaline

Compound	Biological test[a]	
	Trachea	Left auricle
Racemate	0.8	0.09[c]
(−) isomer	1.6 ± 0.3	0.034 ± 0.003[c]
(+) isomer	0.0071[b]	Inactive[d]

[a] Effect relative (−)-adrenaline. The weight comparisons for the compounds are made on the base forms. [b] Partial agonist. [c] See ref 10. [d] Guinea pig heart. See ref 11.

The β-adrenoceptor-stimulating effect was tested on the left auricle (electrically driven) and on spirally cut trachea of the guinea pig[8-10] (Table I).

The (−) isomer has been found to be about 200 times more potent than the (+) isomer for the β_2 receptors. Since the latter was found to be a partial agonist, this value is uncertain.

Experimental Section

The melting points were observed with a microscope and are corrected. Optical rotations were measured with a Perkin-Elmer Model 141 automatic polarimeter in MeOH at 20°. The compounds gave satisfactory uv and ir spectral data, obtained with a Beckman DK2 and a Unicam SP 200 G instrument, respectively.

1-(3',5'-Dibenzyloxyphenyl)-2-(benzyl-*tert*-butylamino)ethanol (2). This compd was prepared by condensing 3,5-dibenzyloxy-ω-bromoacetophenone with benzyl-*tert*-butylamine in EtOH and dry C_6H_6. The product was then reduced with $NaBH_4$ in EtOH and worked up in the usual way.[12] The product, mp 78–79°, was obtained in 86% yield from the amino ketone.

Resolution of 1-(3',5'-dibenzyloxyphenyl)-2-(benzyl-*tert*-butylamino)ethanol (2). To a hot soln of racemic **2** (25.0 g, 0.05 mole) in MeOH (375 ml) was added (−)-dibenzoyltartaric acid monohydrate[13-15] (19.0 g, 0.05 mole) in MeOH (125 ml). The mixture was refluxed for 30 min. After evaporation, the residual oil was dissolved in boiling *i*-PrOH and H_2O added until turbidity appeared, followed by a few ml of *i*-PrOH to get a clear soln. The soln was left overnight, and a white cryst product was obtained. This product was recrystd (6 times) from EtOH until the rotation remained const: [α]D −34.2° (*c* 1.0); yield 4.5 g (10%).

(−)-1-(3',5'-Dihydroxyphenyl)-2-(*tert*-butylamino)ethanol Hydrobromide (1). The above-mentioned salt (4.0 g, 0.005 mole) was suspended in H_2O and after addition of NH_4OH, the extraction of the base was performed with Et_2O. HBr (10%) was then added to the Et_2O phase followed by stirring for 1.5 hr. The white cryst product formed was filtered and washed with H_2O and Et_2O to give the hydrobromide of **2**: [α]D +33.3° (*c* 1.0).

This product was dissolved in EtOH (75 ml), 10% Pd/C (0.15 g) was added, and the hydrogenation was performed at room temp for 4 hr and 70 psig. The catalyst was filtered off, and the residue evaporated to dryness. A small amount of EtOH was added to dissolve the product, and then Et_2O was added until turbidity appeared. The cryst ppt was collected and dried (boiling toluene) for 7 hr: [α]D −34.6° (*c* 1.0); yield 1.2 g (86%); mp 241–242°. *Anal.* ($C_{12}H_{19}NO_3 \cdot HBr$) C, H, Br, N.

(+)-1-(3',5'-Dihydroxyphenyl)-2-(*tert*-butylamino)ethanol Hydrobromide (1). The base of **2** (23.7 g, 0.048 mole), derived from the collected supernatants from the preparation of the (−)-**2**, was dissolved in MeOH (250 ml), (+)-dibenzoyltartaric acid (18.2 g, 0.048 mole) in MeOH (250 ml) was added, and the mixture was refluxed for 60 min. The product was then worked up in the same way as described above and recrystd twice from EtOH to give the (+)-dibenzoyltartrate of **2**: [α]D +34.3° (*c* 1.0); yield 10.5 g (25%). The HBr of **2** was prepared from the tartrate in the same way as described above: [α]D −33.0° (*c* 1.0); yield 6.2 g (89%). The hydrogenation of the HBr of **2** (5.5 g, 0.010 mole) was performed as earlier described. Crystallization was from EtOH–Et_2O: [α]D +34.2° (*c* 1.0); yield 2.7 g (93%); mp 241–243°. *Anal.* ($C_{12}H_{19}NO_3 \cdot HBr$) C, H, Br, N.