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A Conformational Study of Catecholamine Receptor Sites. 5. Syntheses of *dl*-3-Amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalol Hydrochlorides[1]

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The syntheses of the four possible *dl*-3-amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalol hydrochlorides (**1**–**4**) are described. The results of O-methylation by catechol-*O*-methyltransferase (COMT) of these norepinephrine analogs are discussed.

Incorporation of the acetylcholine moiety[3] and the β-phenethanolamine moiety[4] in the conformationally rigid *trans*-decalin system has provided support for the basic postulate that different conformations of a biologically active agent might be preferred at each type of receptor site (metabolic, effector, transport, etc.).

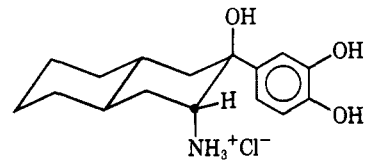
The application of a similar system to the catecholamines provides a method of determining the stereochemical requirements of the α- and β-adrenergic receptors, as well as of the enzymes responsible for the biosynthesis and metabolism of naturally occurring catecholamines.

The synthesis and preliminary testing of the four *dl* pairs of isomeric 3-amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalol hydrochlorides (**1**, **2**, **3**, **4**) provided 8 of the possible 12 skew forms of α-methylnorepinephrine in a conformationally rigid state and are the subject of this report.

The synthesis of the four conformationally rigid systems **1**, **2**, **3**, and **4** required the use of benzyl ether protecting groups on the highly reactive catechol hydroxyls. *o*-Dibenzyloxybenzene (**5**) was prepared according to the procedure of Pines, *et al.*[5] Treatment of **5** with NBS in CCl_4 afforded 3,4-dibenzyloxybromobenzene (**6**).[5] Formation of the corresponding 3,4-dibenzyloxyphenylmagnesium bromide followed by reaction with *trans*-2-decalone afforded the carbinol **7**, which could be dehydrated using either *p*-TsOH or $KHSO_4$ in benzene to afford the desired Δ^2-olefin **8**.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**10**) was prepared by treatment of olefin **8** with NBS in aq dioxane to form the bromohydrin **9**, which was converted into the epoxide **10** by treatment with KOH in aq dioxane. The epoxide **10**, on treatment with liq NH_3 under pressure, afforded the trans diaxial amino alcohol **11**, which on hydrogenation using 10% Pd/C, followed by formation of the HCl salt, afforded **1**. The nmr spectrum of **1** showed C-3 methine absorption of δ 4.41 ($W_{1/2}$ = 7.5 Hz) indicative of an equatorial orientation of the C-3 methine proton.

An alternate pathway to **1** involved the intermediate preparation of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol (**12**). Treatment of epoxide **10** with 0.8 *N* H_2SO_4 in 75% aq DMSO afforded **12** and 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone. Treatment of **12** with *p*-TsCl in pyridine yielded the corresponding tosylate **13**. The tosylate function of **13** was displaced



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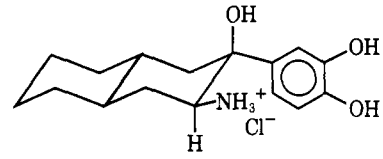

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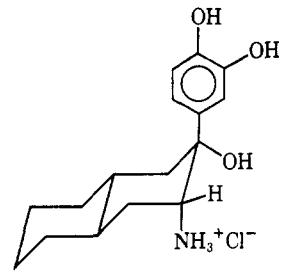

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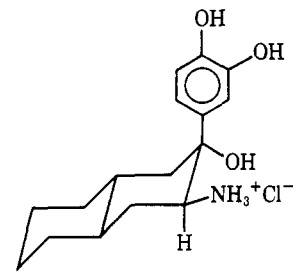

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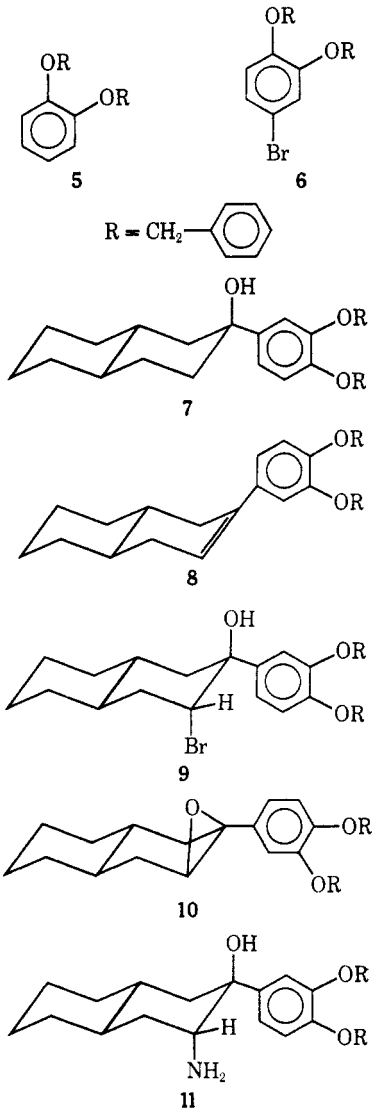
(1) Presented in part before the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, Japan, July 9, 1970.

(2) Taken in part from the dissertation presented by R. T. Borchardt, April 1970, to the Graduate School of the University of Kansas, Lawrence, Kansas, in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

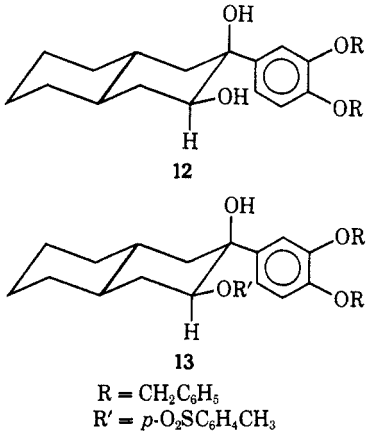
(3) E. E. Smissman, W. L. Nelson, J. B. LaPidus, and J. Day, *J. Med. Chem.*, **9**, 458 (1966).

(4) E. E. Smissman and W. H. Gastrock, *ibid.*, **11**, 860 (1968).

(5) S. H. Pines, S. Karady, and M. Sletzinger, *J. Org. Chem.*, **33**, 1759 (1968).



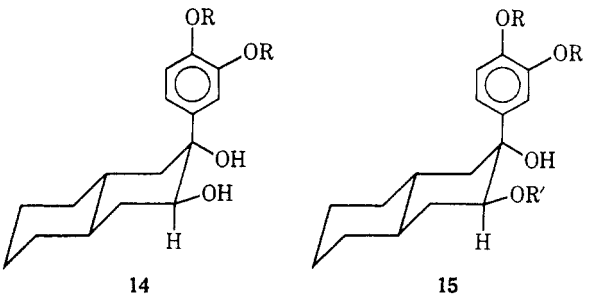
using NH_3 under pressure to yield **11**, which on removal of the benzyl ether protecting groups followed by formation of the HCl salt afforded **1**.



R = $CH_2C_6H_5$
R′ = p-$O_2SC_6H_4CH_3$

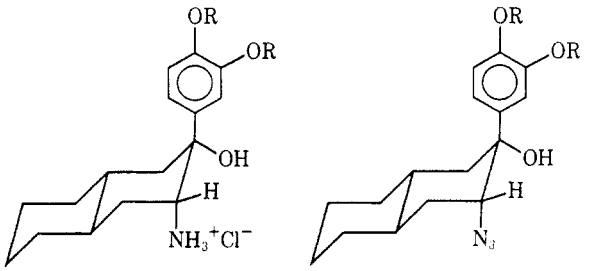
The epoxide **10** was opened using 0.02 N H_2SO_4 in 75% aq DMSO to yield 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol (**14**). The corresponding mesylate **15** was prepared by treatment of **14** with MesCl in pyridine.

The mesylate **15** was utilized in the preparation of 3(a)-amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-3(e)decalol·HCl (**3**). The treatment of **15** with NH_3 under pressure afforded 3(a)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol which was isolated as the HCl salt **16**.



R = $C_6H_5CH_2$
R′ = SO_2CH_3

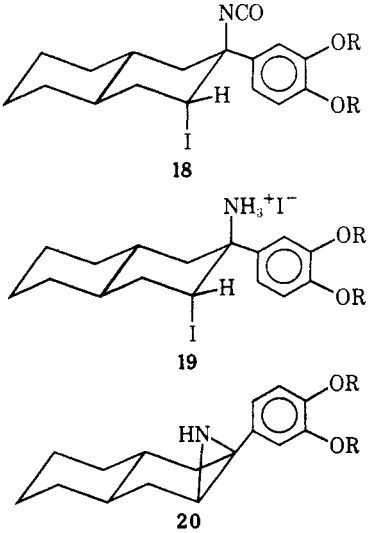
An alternate pathway to **16** involved the formation of the intermediate azide **17** by reaction of mesylate **15** with NaN_3 in DMF. The reduction of **17** using LAH afforded higher overall yields of **16**.



R = $CH_2C_6H_5$

The removal of the benzyl ether protecting groups was accomplished by hydrogenation of **16** using 10% Pd/C to yield **3**. The nmr spectrum of **3** showed **CH** absorption at δ 4.68 ($W_{1/2}$ = 7 Hz) indicative of an equatorial orientation of the C-3 methine proton.

A key intermediate in the synthesis of amino alcohols **2** and **4** was 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2,3-imine (**20**). Preparation of imine **20** involved the general procedure of Hassner and Heathcock.[6,7] The olefin **8** was treated with iodine isocyanate to yield the corresponding isocyanate **18** which on hy-



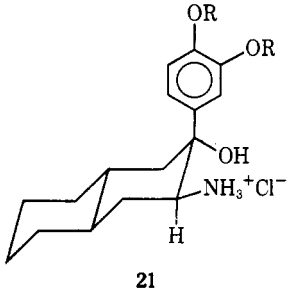
(6) A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).
(7) A. Hassner, M. E. Lorber, and C. Heathcock, *ibid.*, **32**, 540 (1967).

drolysis, using HI in acetone, afforded the desired amine **19**. Cyclization of **19** to the desired imine **20** was accomplished using KOH in MeOH.

Treatment of imine **20** with 1.0 *N* H_2SO_4 in 75% aq DMSO afforded, after separation and formation of the HCl salts, the desired amino alcohols **21** and **22** in 38 and 36% yield, respectively. Utilizing only 1 molar equiv of H_2SO_4 in 75% aq DMSO, imine **20** yielded **21** as the major product.

Hydrogenolysis of the benzyl ether protecting groups of **21** afforded the desired 3(e)-amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-2(e)-decalol·HCl (**4**). The nmr spectrum of **4** exhibited CH absorption at δ 3.22 ($W_{1/2}$ = 18 Hz). The peak half-width was indicative of an axial C-3 methine proton.

Removal of the benzyl protecting groups from **22** afforded the desired 3(e)-amino-2(e)-(3,4-dihydroxyphenyl)-*trans*-2(a)-decalol·HCl (**2**). The nmr spectrum of **2** showed CH absorption at δ 3.25 ($W_{1/2}$ = 16 Hz) indicative of the C-3 methine proton.



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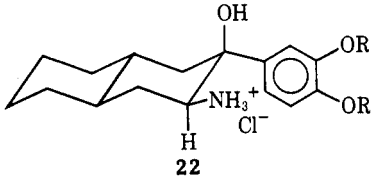

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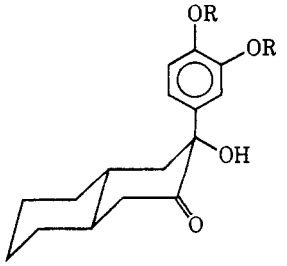
R = $CH_2C_6H_5$

An alternate pathway and further structure proof for **21** was achieved by oxidation of **14** to 2(a)-(3,4-dibenzyloxyphenyl)-2(e)-hydroxy-*trans*-3-decalone (**23**) utilizing the procedures of Pfitzner and Moffatt[8] or Holum.[9] Conversion of ketone **23** into the corresponding oxime **24** followed by reduction using bis(2-methoxyethoxy)-aluminum hydride according to the procedure of Bazent, *et al.*,[10] afforded **21**. This reduction was stereoselective, and no axial amino function was detected. LAH reduction of **24** was less stereoselective and yielded a mixture of **16** and **21**.



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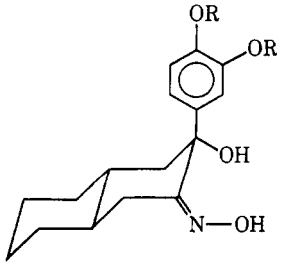

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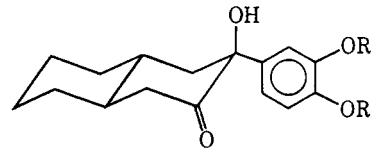
Similarly, an alternate pathway and further structure proof for **22** was achieved by oxidation of **21** to 2(e)-(3,4-dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone (**25**) according to the procedure of Pfitzner and Moffatt.[8] Conversion of **25** into the oxime **26** followed by reduction using sodium bis(2-methoxyethoxy)aluminum hydride[9] afforded, after separation, amines **11** and **22**.



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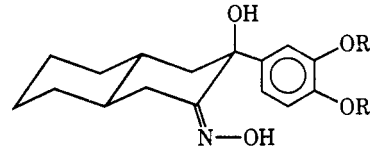

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The reduction of oximes **24** and **26** was inferior to the imine opening method as a pathway to amines **21** and **22**, respectively.

Biological Results.—Table I lists the observed rates and relative rates of O-methylation by catechol-*O*-methyltransferase[11] (COMT) of the α-methylnorepinephrine analogs **1**, **2**, **3**, and **4**. Table II lists the K_m, V_{max}, and relative V_{max} values determined for the same substrates as compared to norepinephrine.

TABLE I

CATECHOL-*O*-METHYLTRANSFERASE[a] RATES OF O-METHYLATION OF α-METHYLNOREPINEPHRINE ANALOGS

Compd	Conformation: NH_2	Conformation: OH	Conformation: Aryl	nmoles of product/10 min[d]	Relative rates
1[b]	a	a	e	79.6	11.32
2[b]	e	a	e	21.6	3.07
3[b]	a	e	a	3.29	0.47
4[b]	e	e	a	3.12	0.45
L-Norepinephrine[c]				7.03	1.00

[a] Assay conditions: the assay mixts contained the following components (in μmoles) added in this sequence: H_2O, so that the final vol was 0.5 ml; $MgCl_2$ (1.0); sodium phosphate buffer, pH 8.0 (50); *S*-adenosyl-L-methionine (0.5); 0.1 μCi of *S*-adenosyl-L-methionine-^{14}C and substrate (0.1). Final substrate concn was 2.0×10^{-4} *M*. Enzyme preparation, purified by procedure of B. Nikadejevic, S. Senoh, J. W. Daly, and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, **174**, 83 (1970), contained 8.7 mg of protein per ml. The reaction was started by the addition of substrate and incubated for 10 min at 37°. The reaction was stopped by addition of 0.5 ml of 0.5 *M* borate buffer, pH 10.0, and the mixt was extd with 10 ml of PhMe–*i*-AmOH (3:2). Following centrifugation, an aliquot (5 ml) of the organic phase was transferred to a scintillation vial, a dioxane-based phosphor solution (10 ml) was added, and the radioactivity was measured in a scintillation spectrophotometer. The results were corrected for blank values obtained by carrying out the reaction without substrate. [b] Hydrochloride salt. [c] Bitartrate salt. [d] Enzyme, 0.1 ml per assay.

The preliminary enzymatic data indicates that the conformation where the amino group and OH group have a dihedral angle of 180° best fits the active site on COMT. This is apparent from the relative rate and

(8) E. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5670 (1965).
(9) J. F. Holum, *J. Org. Chem.*, **26**, 4914 (1966).
(10) V. Bazent, M. Capka, M. Cerny, V. Chvalovsky, K. Kochloefl, M. Kraus, and J. Malek, *Tetrahedron Lett.*, 3303 (1968).
(11) B. Nikadejevic, S. Senoh, J. W. Daly, and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, **174**, 83 (1970).

TABLE II

CATECHOL-*O*-METHYLTRANSFERASE. K_m AND V_{max} OF α-METHYLNOREPINEPHRINE ANALOGS[a]

Compd	Conformation NH₂	OH	Aryl	$K_m \times 10^{-4}$	V_{max}, nmoles of product/10 min[d,e]	Relative V_{max}
1[b]	a	a	e	5.46	304.7	3.06
2[b]	e	a	e	4.55	72.0	0.72
3[b]	a	e	a	31.4	54.2	0.54
4[b]	e	e	a	5.37	11.2	0.11
L-Norepinephrine[c]				26.2	99.7	1.00

[a] Assay conditions: the assay procedure was identical with that described in Table I except that final substrate concns ranged from 3.0×10^{-4} to 0.4×10^{-4} *M*. The K_m and V_{max} values were obtained from a least-squares analysis of plotting $1/V$ *vs.* $1/S$. [b] Hydrochloride salt. [c] Bitartrate salt. [d] Enzyme, 0.1 ml per assay. [e] Correlation coefficients > 0.996.

V_{max} for compound **1**. Considerably slower rates of O-methylation were observed for **3** and **4**.

Experimental Section[12]

***trans*-2-Decalone.**—Commercially available *trans*-2-decalol (81.0 g, 0.53 mole) was oxidized according to the procedure of Smissman, *et al.*,[3] utilizing Jones reagent to yield 71.8 g (90%), oxime mp 74.5–76° (lit.[13] mp 76°).

3,4-Dibenzyloxybenzene (5).—According to the procedure of Pines, *et al.*,[5] **5** was prepd by reaction of catechol (55.0 g, 0.5 mole), anhyd K_2CO_3 (172.5 g, 1.25 moles), and $PhCH_2Cl$ (158.0 g, 1.25 moles) and Me_2CO as a solvent to yield 90.5 g (62%), mp 60–62° (lit.[5] mp 61.5°).

3,4-Dibenzyloxybromobenzene (6).—3,4-Dibenzyloxybromobenzene was prepd according to the procedure of Pines, *et al.*,[5] using *o*-dibenzyloxybenzene (**5**) (10.30 g, 0.355 mole) and NBS (69.4 g, 0.39 mole) and CCl_4 as a solvent to yield 90.0 g (67%), mp 64–66° (lit.[5] mp 65.5–66.5°).

2-(3,4-Dibenzyloxyphenyl)-Δ²-*trans*-octalin (8).—The Grignard reagent was prepared by refluxing 3,4-dibenzyloxybromobenzene (**6**) (76.0 g, 0.206 mole) in 200 ml of anhyd THF with 5.35 g (0.22 g-atom) of Mg turnings. After 3–4 hr most of the Mg was dissolved, and tlc indicated the absence of starting material.

trans-2-Decalone (29.0 g, 0.19 mole) in 100 ml of anhyd Et_2O was added dropwise over a 30-min period to the Grignard reagent. The reaction mixt was stirred at 25° for 3 hr after which a satd NH_4Cl soln was added dropwise. The H_2O layer was washed several times with Et_2O, the combined Et_2O fractions were washed with satd NH_4Cl soln and H_2O and dried ($MgSO_4$), and the Et_2O was removed. The residue was dissolved in 1 l. of C_6H_6, and 48.5 g of $KHSO_4$ was added. The mixt was heated at reflux for 15 hr using a Dean–Stark trap to collect the H_2O. The $KHSO_4$ was removed by filtration, and the solvent was removed to afford 90.5 g of an oil. Chromatography on silica gel by eluting with 5% EtOAc–hexane afforded, after recrystn (hexane), 38.2 g (47.5%) of **8**: mp 76–77.5°; nmr ($CDCl_3$) δ 7.60–6.80 (m, 13 H, arom), 5.95 (m, 1 H, $W_{1/2}$ = 10 Hz, vinyl C=C**H**), 5.10 (s, 4 H, benzylic). *Anal.* ($C_{30}H_{32}O_2$) C, H.

3(a)-Bromo-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (9). A. *N*-Bromoacetamide Procedure.—To 2-(3,4-dibenzyloxyphenyl)-Δ²-*trans*-octalin (**8**) (24.9 g, 56.5 mmoles) in 800 ml of Me_2CO was added 25 ml of H_2O which contd a catalytic amount of H_2SO_4 and *N*-bromoacetamide (8.97 g, 65 mmoles). The reaction mixt was stirred at 10–15° for 6 hr after which the vol of Me_2CO was reduced to 150 ml. The cryst product was removed by filtration and washed with 50 ml of cold Me_2CO to yield 19.4 g (66%) of **9**, mp 141–145°. A sample for analysis was prepd by recrystn (Me_2CO): mp 147–148°; nmr (DMSO-d_6) δ 7.60–6.95 (m, 13 H, arom), 5.10 (s, 4 H, benzylic), 4.50 (m, 1 H, $W_{1/2}$ = 6 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{33}O_3Br$) C, H.

B. NBS Procedure.—To 2-(3,4-dibenzyloxyphenyl)-Δ²-*trans*-octalin (**8**) (6.00 g, 14 mmoles) in 600 ml of dioxane was added a soln of H_2SO_4 (6.00 g, 60 mmoles) in 60 ml of H_2O with cooling. The reaction mixt was cooled to 10° and NBS (10.68 g, 60 mmoles) in 50 ml of dioxane was added. The reaction mixt was stirred at 10–15° for 4 hr after which 600 ml of H_2O was added. The aq soln was stirred at 0° for 1 hr after which the cryst product was collected by filtration, washed with 50 ml of cold Me_2CO, and dried to yield 22.4 g (75%) of **9**, mp 142–145°. Recrystn was not required and when attempted it often resulted in decompn of **9**.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin 2,3-Oxide (10).—To 3(a)-bromo-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (**9**) (6.00 g, 11.5 mmoles) in 250 ml of dioxane was added dropwise with cooling a soln of KOH (1.00 g, 16.0 mmoles) in 20 ml of H_2O. The soln was allowed to stir for 3 hr at 10–15°. Excess H_2O was added, and the aq soln was extd several times with C_6H_6. The combined C_6H_6 fractions were washed with H_6O, satd NH_4Cl soln, and satd NaCl soln and dried ($MgSO_4$). The C_6H_6 was removed to yield 5.60 g of cryst material. Recrystn (Me_2CO–hexane) afforded 4.55 g (89%) of **10**: mp 95.5–97.5°; nmr ($CDCl_3$) δ 7.60–6.80 (m, 13 H, arom), 5.12 (s, 4 H, benzylic), 3.04 (d, 1 H, *J* = 5 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{32}O_3$) C, H.

3(a)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (11). A. From 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin 2,3-Oxide (10).—2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**10**) (1.10 g, 2.50 mmoles) was placed in a steel reaction vessel, cooled in Dry Ice–Me_2CO, and *ca.* 100 ml of liq NH_3 was added. The vessel was sealed and heated at 155° for 24 hr after which it was cooled in a Dry Ice–Me_2CO bath, the vessel was opened, and the NH_3 was allowed to evap. The residue was dissolved in $CHCl_3$ and filtered. The $CHCl_3$ was removed to yield 1.40 g of a yellowish oil. Chromatography on silica gel ($CHCl_3$) afforded 0.650 g of a semisolid material. Recrystn ($CHCl_3$–hexane) afforded 0.525 g (46%) of **11**: mp 120–121°; ir (KBr) 3550, 3330 (OH), 3230, 3190 cm^{-1} (amine NH); nmr ($CDCl_3$) δ 7.60–6.95 (m, 13 H, arom), 5.15 (s, 4 H, benzylic), 3.08 (m, 1 H, $W_{1/2}$ = 8.5 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{33}NO_3$) C, H, N.

B. From 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),-3(e)-diol 3(e)-Tosylate (13).—2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol 3(e)-tosylate (**13**) (0.120 g, 0.195 mmole) was placed in a steel reaction vessel and cooled as above, and *ca.* 50 ml of liq NH_3 was added. After heating at 150–160° for 24 hr, and work-up as above, the $CHCl_3$ was removed to yield 0.125 g of a yellowish oil. Thick-layer chromatography on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded, after recrystn ($CHCl_3$–hexane), 0.055 g (61.5%) of **11**, mp 120–121°.

3(a)-Amino-2(e)-(3,4-dihydroxyphenyl)-*trans*-2(a)-decalol·HCl (1).—To 3(a)-amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (**11**) (0.230 g, 0.5 mmole) in 10 ml of anhyd MeOH was added 60 mg of 10% Pd/C under N_2. The mixt was hydrogenated at 25° at 1 atm, and the reaction was stopped after consumption of the theoretical amount of H_2. The reaction mixt was neutralized with dry HCl, and the catalyst was removed by filtration. The solvent was removed to yield a semisolid product. Recrystn (EtOH–Et_2O) afforded 125 mg (80%) of **1**: mp 238–241° dec; nmr (CD_3OD) δ 7.02–6.84 (m, 3 H, arom), 4.41 (m, 1 H, $W_{1/2}$ = 7.5 Hz, C-3 C**H**). *Anal.* ($C_{16}H_{24}NO_3Cl$) C, H, N.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol (12).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**10**) (2.20 g, 5.00 mmoles) in 75 ml of DMSO was added a soln of H_2SO_4 (4.0 g) in 25 ml of H_2O. The reaction mixt was allowed to stir at 25° for 24 hr. H_2O was added, and the resulting ppt was removed by filtration. The ppt was dissolved in $CHCl_3$, the $CHCl_3$ soln was dried ($MgSO_4$), and the solvent was removed to afford 2.45 g of a semisolid material. Chromatography on silica gel ($CHCl_3$) afforded 3 major fractions.

Fraction A. 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone.—Recrystn (Me_2CO–hexane) afforded 0.550 g (21.5%): mp 117–118°; ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.60–6.60 (m, 13 H, arom), 5.05 (s, 4 H, benzylic), 3.50 (q, 1 H, J_{aa} = 11 Hz, J_{ae} = 6 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{32}O_3$) C, H.

Fraction B. Impure 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone was purified by formation of the oxime. Recrystn ($CHCl_3$–EtOAc) afforded 0.540 g (21%) of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone oxime: mp 204–206°; nmr ($CDCl_3$) δ 7.55–6.80 (m, 13 H, arom), 5.15 (s, 4 H, benzylic), 3.34 (m, 1 H, $W_{1/2}$ = 17 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{33}NO_3$) C, H, N.

(12) Melting points were obtained on a calibrated Thomas-Hoover Uni-Melt and are corrected. Ir data were recorded on Beckman IR 10 and Perkin-Elmer 421 spectrophotometers, and nmr data on a Varian Associates Model A-60 A spectrophotometer (TMS). Microanalyses were conducted by Midwest Microlab, Inc., Indianapolis, Ind., on the F & M Model 185 C, H, N analyzer, University of Kansas, Lawrence, Kan., and by the Microanalytical Laboratory, National Institutes of Health, Bethesda, Md. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(13) W. Huckel, *Justus Liebigs Ann. Chem.*, **441**, 1 (1925).

Fraction C. 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol (12).—Recrystn (Me_2CO) afforded 0.520 g (19.5%) of **12**: mp 170–171°; nmr ($CDCl_3$) δ 7.60–6.95 (m, 13 H, arom), 5.17 (2 s, 4 H, benzylic), 3.98 (m, 1 H, $W_{1/2}$ = 17.5 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{34}O_4$) C, H.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol 3-Tosylate (13).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol (**12**) (0.200 g, 0.435 mmole) dissolved in 5 ml of C_6H_5N was added *p*-TsCl (0.125 g, 0.66 mmole). The mixt was allowed to stir at 25° for 24 hr, after which H_2O was added. The resulting crystals were removed by filtration and dissolved in $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$), and the $CHCl_3$ was removed to yield 0.220 g of a solid product. Repeated recrystn (Me_2CO–hexane) afforded 0.125 g (47.5%) of **13**: mp 111–112; ir (KBr) 3538 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.60–6.73 (m, 13 H, arom), 5.12 (s, 2 H, benzylic), 4.97 (s, 2 H, benzylic), 4.85 (m, 1 H, C-3 C**H**), 2.25 (s, 3 H, aryl C**H**$_3$). *Anal.* ($C_{37}H_{40}O_6S$) C, H.

2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol (14).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**10**) (2.20 g, 5.0 mmoles) in 225 ml of DMSO was added a soln of H_2SO_4 (0.300 g) in 75 ml of H_2O (total of 0.02 *N* H_2SO_4). The mixt was allowed to stir at 25° for 3 hr after which H_2O was added. The H_2O layer was extd several times with C_6H_6, and the combined C_6H_6 fractions were washed with H_2O and satd NaCl soln. The C_6H_6 soln was dried ($MgSO_4$), and the C_6H_6 was removed to afford 2.45 g of a yellowish oil. Crystn (Me_2CO–hexane) afforded 1.50 g (66%) of **14**: mp 132–133°; ir (KBr) 3600–3410 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.55–6.88 (m, 13 H, arom), 5.12 (2 s, 4 H, benzylic), 3.80 (m, 1 H, $W_{1/2}$ = 18.5 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{34}O_4$) C, H.

2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-2(e),3(e)-diol 3(e)-Mesylate (15).—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(e),-3(e)-diol (**14**) (1.00 g, 2.2 mmoles) in 15 ml of anhyd C_6H_5N, cooled in an ice bath, was added MesCl (0.350 g, 3.00 mmoles) in 2 ml of anhyd C_6H_5N. The mixt was stirred at 25° for 24 hr after which H_2O was added. The aq layer was extd several times with C_6H_6, and the combined C_6H_6 fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$). The C_6H_6 was removed to yield 1.15 g of a colorless oil: ir (neat) 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 5.20 (2 s, 4 H, benzylic), 4.83 (m, 1 H, $W_{1/2}$ = 17 Hz, C-3 C**H**), 3.00 (s, 3 H, mesylate C**H**$_3$). The crude mesylate was utilized without further purification.

3(a)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (16). A. NH_3 Procedure.—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol 3(e)-mesylate (**15**) (1.14 g, 2.18 mmoles) in a steel reaction vessel cooled in a Dry Ice–Me_2CO bath was added *ca.* 100 ml of liq NH_3. The procedure utilized was similar to that employed for **11** to yield 1.05 g of a red oil. Chromatography on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded a colorless oil, 0.520 g. Formation of the HCl salt and recrystn (EtOH–EtOAc) afforded 0.325 g (31%) of **16**: mp 201–203°; nmr ($CDCl_3$, free base) δ 7.60–6.78 (m, 13 H, arom), 5.16 (2 s, 4 H, benzylic), 4.21 (m, 1 H, $W_{1/2}$ = 8.0 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{36}ClNO_3$) C, H, N.

B. Azide Procedure.—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol 3(e)-mesylate (**15**) (1.70 g, 3.25 mmoles) in 100 ml of DMF was added a soln of NaN_3 (1.00 g, 15.4 mmoles) in 15 ml of H_2O. The mixt was heated to 90–100° for 5 hr, after which H_2O was added, and the aq layer was extd with Et_2O. The combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$) and the solvent was removed to yield 1.55 g of **17**: ir (neat) 2110 cm^{-1} (azide); nmr ($CDCl_3$) δ 4.27 (m, 1 H, $W_{1/2}$ = 7 Hz, C-3 C**H**).

A soln of LAH (0.500 g, 13.2 mmoles) in 50 ml of anhyd EtO_2 was refluxed for 2 hr, after which the crude **17** in 50 ml of anhyd Et_2O was added at such a rate as to maintain reflux. The mixt was stirred at 25° for 2 hr, after which "wet" Et_2O followed by H_2O was added to decompose excess LAH. The aq layer was extd several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the solvent was removed to yield a colorless oil. Formation of the HCl salt and recrystn EtOH(–EtOAc) afforded 0.55 g (35%) of **16**, mp 200–202°.

3(a)-Amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-2(e)-decalol·HCl (3).—To 3(a)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (**16**) (0.180 g, 0.365 mmole) in 10 ml of anhyd MeOH was added 40 mg of 10% Pd/C under N_2. The mixt was hydrogenated at 25° as in the preparation of **1** to afford 105 mg (91%) of **3**: mp 179–181° (1 mole of MeOH of crystn); nmr (CD_3OD) δ 7.14–6.86 (m, 3 H, arom), 4.68 (m, 1 H, $W_{1/2}$ = 7 Hz, C-3 C**H**), 3.35 (s, 3 H, C**H**$_3$OH of crystn). *Anal.* ($C_{17}H_{28}ClNO_4$) C, H, N.

2(e)-(3,4-Dibenzyloxyphenyl)-3(a)-iodo-*trans*-decalin 2(a)-Isocyanate (18).—To 2-(3,4-dibenzyloxyphenyl)-Δ^2-*trans*-octalin (**8**) (10.35 g, 24.0 mmoles) in 60 ml of THF and 60 ml of Et_2O was added freshly prepared AgNCO[6,7] (10.95 g, 72.0 mmoles). The suspension was cooled in an ice–salt bath while being stirred. When the slurry had cooled to −15°, solid I_2 (6.18 g) was added, and stirring was continued for 2 hr in the cold and then for 6 hr at 25°. The Et_2O soln was filtered through Celite 545 to remove the yellow inorg salts, and the solvent was removed. Crystn (Me_2CO–hexane) afforded 9.30 g (65%) of **18**: mp 133–134°; ir ($CHCl_3$) 2259 cm^{-1} (N=C=O); nmr ($CDCl_3$) δ 7.60–6.87 (m, 13 H, arom), 5.20 (s, 2 H, benzylic), 5.15 (s, 2 H, benzylic), 4.61 (m, 1 H, $W_{1/2}$ = 6 Hz, C-3 C**H**). *Anal.* ($C_{31}H_{32}INO_3$) C, H, N.

2(a)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-3(a)-iodo-*trans*-decalin·HI (19).—To a soln of 2(e)-(3,4-dibenzyloxyphenyl)-3(a)-iodo-*trans*-decalin 2(a)-isocyanate (**18**) (2.57 g, 4.3 mmoles) in 200 ml of Me_2CO was added 25 ml of 57% HI. The mixt was stirred at 25° for 1.5 hr, after which 250 ml of H_2O was slowly added with cooling. The aq soln was stirred at 0° for 2 hr, after which the cryst product was removed by filtration. Recrystn (Me_2CO) afforded 2.36 g (79%) of **19**: mp 110–112°; nmr (CD_3OD) δ 7.60–7.30 (m, 13 H, arom), 5.22 (s, 2 H, benzylic), 5.17 (s, 2 H, benzylic), 5.18 (m, 1 H, C-3 C**H**). *Anal.* ($C_{30}H_{35}NO_2I_2$) C, H, N.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2,3-imine (20).—A suspension of 2(a)-amino-2(e)-(3,4-dibenzyloxyphenyl)-3(a)-iodo-*trans*-decalin·HI (**19**) (2.36 g, 3.3 mmoles) in 100 ml of 1.0 *N* methanolic KOH was stirred at 25° for 4 hr. H_2O was added, and the suspension was extd several times with Et_2O. The combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$). The desiccant was removed by filtration, and the solvent was removed *in vacuo*. Crystn (Et_2O–hexane) afforded 1.22 g (87%) of **20**: mp 85–87°; ir ($CHCl_3$) 3300 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.58–6.81 (m, 13 H, arom), 5.14 (s, 2 H, benzylic), 5.10 (s, 2 H, benzylic), 2.25 (m, 1 H, $W_{1/2}$ = 5 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{33}NO_2$) C, H, N.

3(e)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (21) and 3(e)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol·HCl (22).—To a soln of H_2SO_4 (60.0 g) in 112 ml of H_2O and 250 ml of DMSO was added dropwise with cooling (0°) a soln of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2,3-imine (**20**) (6.00 g, 14.6 mmoles) in 100 ml of DMSO (total of 1.0 *N* H_2SO_4). The mixt was stirred at 25° for 24 hr, after which a 5% NaOH soln was added to neutralize excess H_2SO_4. The aq layer was extd several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the Et_2O was removed to yield colorless oil. Chromatography on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded 2 major fractions.

Fraction A. 3(e)-Amino-2(e)-(3′,4′-dibenzyloxyphenyl)-*trans*-2(a)-decalol (22).—Formation of HCl salt and recrystn (MeOH–Et_2O) afforded 2.40 g (36%) of **22**: mp 233–235° (free base, mp 156–157°); nmr (free base, $CDCl_3$) δ 7.55–6.85 (m, 13 H, arom), 5.18 (s, 2 H, benzylic), 5.11 (s, 2 H, benzylic), 3.12 (m, 1 H, $W_{1/2}$ = 18 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{35}NO_3$) C, H, N.

Fraction B. 3(e)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol (21).—Formation of HCl salt and recrystn (MeOH–Et_2O) afforded 2.49 g (38%) of **21**: mp 200–202°; nmr ($CDCl_3$, free base) δ 7.53–6.73 (m, 13 H, arom), 5.20 (s, 2 H, benzylic), 5.15 (s, 2 H, benzylic), 2.85 (m, 1 H, $W_{1/2}$ = 20 Hz, C-3 C**H**). *Anal.* ($C_{30}H_{36}ClNO_3$) C, H, N.

3(e)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (21).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin-2,3-imine (**20**) (1.00 g, 2.3 mmoles) in 75 ml of DMSO was added a soln of H_2SO_4 (0.250 g, 2.5 mmoles) in 25 ml of H_2O. The mixt was allowed to stir at 25° for 3 hr, after which a 5% NaOH soln was added to neutralize excess H_2SO_4. The aq layer was extd several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$), and the Et_2O was removed to yield a colorless oil. Chromatography on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded 2 major fractions.

Fraction A.—3(e)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (22). Recrystn (MeOH) afforded 0.151 g (14.5%) of **22**, mp 156–157°.

Fraction B.—3(e)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-

2(e)-decalol·HCl (21).—Formation of the HCl salt and recrystn (MeOH–Et_2O) afforded 0.620 g (57%) of **21**, mp 200–202°.

3(e)-Amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-2(e)-decalol·HCl (4).—To 3(e)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (**21**) (1.24 g, 2.5 mmoles) in 30 ml of anhyd MeOH was added 120 mg of 10% Pd/C under N_2. The mixt was hydrogenated as in the preparation of **1** to afford 0.756 g (97%) of **4**: mp 147–149° (1 mole of MeOH of crystn); nmr (CD_3OD) δ 7.29–6.75 (m, 3 H, arom), 3.32 (m, 1 H, C-3 C**H**), 3.34 (s, 3 H, CH_3OH of crystn). *Anal.* ($C_{17}H_{28}ClNO_4$) C, H, N.

3(e)-Amino-2(e)-(3,4-dihydroxyphenyl)-*trans*-2(a)-decalol·HCl (2).—To 3(e)-amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (**22**) (2.40 g, 4.88 mmoles) in 60 ml of anhyd MeOH was added 200 mg of 10% Pd/C under N_2. The mixt was hydrogenated as in the preparation of **1** to yield 1.43 g (96%) of **2**: mp 263–265; nmr (DMSO-d_6) δ 6.98–6.79 (m, 3 H, arom), 3.25 (m, 1 H, $W_{1/2}$ = 16 Hz, C-3 C**H**). *Anal.* ($C_{16}H_{24}ClNO_3$) C, H, N.

2(a)-(3,4-Dibenzyloxyphenyl)-2(e)-hydroxy-*trans*-3-decalone (23). A. Pfitzner–Moffatt Method.[8]—2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol (**14**) (0.458 g, 1.00 mmole) was dissolved in DMSO (2.0 ml) and C_6H_6 (1 ml) contg DCC (0.620 g, 3.0 mmoles). Anhyd *o*-H_3PO_4 (0.010 g, 0.1 mmole) in 0.5 ml of DMSO was added, and the mixt was stirred at 25° for 2 hr. Et_2O (25 ml) was added followed by a soln of oxalic acid (0.270 g, 3.0 mmoles) in MeOH (2.5 ml). After gas evoln had ceased, and the insol dicyclohexylurea was removed by filtration. The Et_2O layer was washed with 5% $NaHCO_3$ soln and H_2O and dried ($MgSO_4$). The solvent was removed to yield 0.475 g of a colorless oil. Chromatography on silica gel, eluting with 5% EtOAc–C_6H_6, afforded 0.201 g (44%) of **23**: ir (neat) 3460 (OH), 1709 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.55–6.59 (m, 13 H, arom), 5.12 (s, 4 H, benzylic). Oxime derivative prepd for analysis had mp 124–125°. *Anal.* ($C_{30}H_{33}NO_4$) C, H, N.

B. Sarett Method.[9]—A slurry of the Sarett complex in anhyd C_6H_5N was prepared by adding CrO_3 (0.163 g, 1.625 mmoles) to vigorously stirred, chilled C_6H_5N (5 ml) over 10–15 min. 2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(e),3(e)-diol (**14**) (0.250 g, 0.544 mmole) in C_6H_5N (1 ml) was added to the slurry. The slurry was allowed to stir for 30 min and then remain at 25° for 15 hr. To the mixt was added EtOAc (20 ml), and the slurry was passed through a Celite–Al_2O_3 column eluting with 100 ml of EtOAc. The EtOAc was removed *in vacuo* to yield a colorless oil. Chromatography on silica gel by eluting with 5% EtOAc–C_6H_6 afforded 0.135 g (54%) of **23**.

2(a)-(3,4-Dibenzyloxyphenyl)-2(e)-hydroxy-*trans*-3-decalone Oxime (24).—2(a)-(3,4-Dibenzyloxyphenyl)-2(e)-hydroxyl-*trans*-3-decalone (**23**) (0.180 g, 0.395 mmole) in 15 ml of EtOH was heated to reflux. To the hot soln was added a soln of NH_2OH·HCl (0.100 g) and NaOAc (0.100 g) in 5 ml of H_2O. The mixt was heated at reflux for 1 hr, after which H_2O was added, and the resulting crystals were collected by vacuum filtration. Recrystn (*n*-PrOH) afforded 0.175 g (94%) of **24**, mp 126–125°. *Anal.* ($C_{30}H_{33}NO_4$) C, H, N.

Reduction of 2(a)-(3,4-Dibenzyloxyphenyl)-2(e)-hydroxy-*trans*-3-decalone Oxime (24).—To a soln of sodium bis (2-methoxyethoxy)aluminum hydride {0.505 g [0.72 g of a 70% C_6H_6 soln (Aldrich)], 2.5 mmoles} in 15 ml of anhyd C_6H_6 was added dropwise a soln of 2(a)-(3,4-dibenzyloxyphenyl)-2(e)-hydroxy-*trans*-3-decalone oxime (**24**) (0.235 g, 0.5 mmole) in 20 ml of C_6H_6. The mixture was refluxed for 1 hr, after which "wet" C_6H_6 followed by H_2O was added to decompose excess hydride. The H_2O layer was extd several times with C_6H_6, and the combined C_6H_6 fractions were washed with H_2O, 5% NaOH soln, and satd NaCl soln. The combined C_6H_6 fractions were dried ($MgSO_4$), and the C_6H_6 was removed to yield a colorless oil, 0.215 g. Thick-layer chromatography by eluting with 7% MeOH–$CHCl_3$ afforded a colorless oil, 0.055 g. Formation of the HCl salt afforded 0.052 g (21%), mp 200–202°. Ir, nmr, and mp were identical with those of previously prepared 3(e)-amino-2(a)-(3′,4′-dibenzyloxyphenyl)-*trans*-2(e)-decalol·HCl (**21**).

2(e)-(3,4-Dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone (25).—2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin-2(a),3(e)-diol (**12**) (0.230 g, 0.5 mmole) was dissolved in DMSO (2.0 ml) and C_6H_6 (2 ml) containing DCC (0.310 g, 1.5 mmoles). Anhyd *o*-H_3PO_4 (0.005 g, 0.05 mmole) in 0.5 ml of DMSO was added, and the mixt was stirred at 25° for 12 hr. Et_2O (25 ml) was added followed by a soln of oxalic acid (0.135 g, 1.5 mmoles) in MeOH (1.5 ml). After gas evoln had ceased, the insol dicyclohexylurea was removed by filtration. The Et_2O layer was washed with 5% $NaHCO_3$ soln and H_2O and dried ($MgSO_4$). The Et_2O was removed to yield 0.210 g of a semisolid product. Recrystn (Me_2CO–hexane) afforded 0.169 g (78%) of **25**: mp 135–136; ir (KBr) 3385 (OH), 1712 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.50–6.85 (m, 13 H, arom) 5.12 (s, 4 H, benzylic). *Anal.* ($C_{30}H_{32}O_4$) C, H.

2(e)-(3,4-Dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone Oxime (26).—2(e)-(3,4-Dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone (**25**) (0.300 g, 0.66 mmole), NH_2OH·HCl (0.200 g), and NaOAc (0.200 g) in 5 ml of H_2O afforded 0.305 g (98%) of **26**, mp 208–210°. *Anal.* ($C_{30}H_{33}NO_4$) C, H, N.

Reduction of 2(e)-(3,4-Dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone Oxime (26).—To a soln of sodium bis(2-methoxy)aluminum hydride {0.505 g [0.72 g of a 70% C_6H_6 soln (Aldrich)], 2.5 mmoles} in 15 ml of anhyd C_6H_6 was added dropwise a soln of 2(e)-(3,4-dibenzyloxyphenyl)-2(a)-hydroxy-*trans*-3-decalone oxime (**26**) (0.267 g, 0.57 mmole) in 20 ml of anhyd THF. The reaction conditions were similar to those used for **24** to yield a yellowish oil, 0.205 g. Thick-layer chromatography by eluting with 4% MeOH–$CHCl_3$ afforded 2 major fractions.

Fraction A. 3(a)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol (11).—Recrystn (Et_2O) afforded 0.022 g (9%) of **11**, mp 117–120°. Ir and mp were identical with those of previously prepd **11**. No depression of mp was observed on admixture of fraction A and **11**.

Fraction B. 3(e)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-2(a)-decalol·HCl (22).—Formation of HCl salt and recrystn (MeOH–Et_2O) afforded 0.019 g (7%), mp 230–233°. Ir and mp were identical with those of previously prepd **22**. No depression of mp was observed on admixture of fraction B and **22**.

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