A Conformational Study of Catecholamine Receptor Sites. 6. Syntheses of *dl*-3-Amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalin Hydrochlorides[1]

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

Investigations in these laboratories on the basic postulate that different conformations of a biologically active agent might be preferred at various types of receptors (metabolic, effector, transport) have led to the study of the biogenetic steps involved in the formation of neutrotransmitter substances as well as to the metabolic methods by which the neurotransmitter or the precursors can be deactivated. Previously, the ACh[3] and β-phenethanolamine[4] moieties have been incorporated into the conformationally rigid *trans*-decalin.

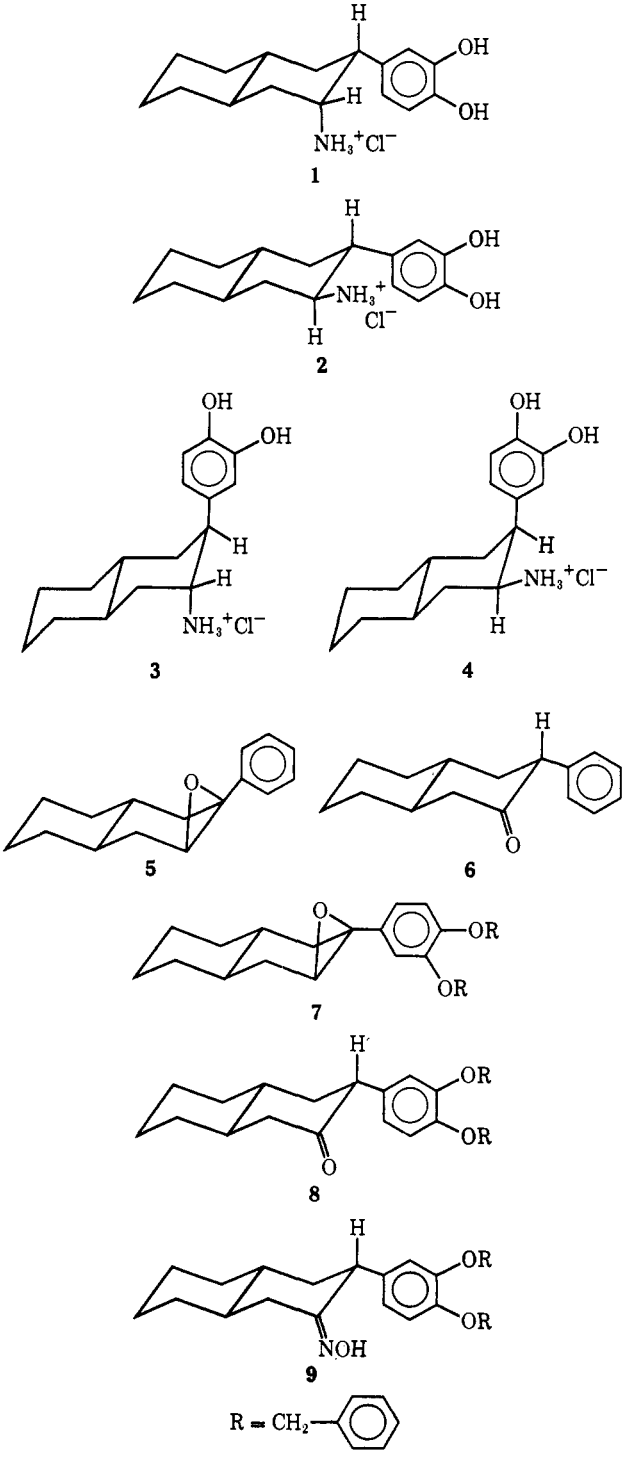
A similar approach was employed in the investigation of the catecholamine receptor sites by the syntheses and preliminary testing of the four *dl* pairs of isomeric 3-amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalol·HCl.[5] This work indicated that the conformation in which the NH_2 group and the OH group have a dihedral angle of 180° best fits the active site of the enzyme, catechol-*O*-methyltransferase.

In an attempt to investigate further the stereochemical requirements of the metabolically important catechol-*O*-methyltransferase, as well as the biosynthetically important dopamine-β-hydroxylase, the syntheses and preliminary testing of the four *dl* pairs of isomeric 3-amino-2-(3,4-dihydroxyphenyl)-*trans*-2-decalin hydrochlorides (**1**, **2**, **3**, **4**) were undertaken.

As a model system, for the investigation of pathways to **1** and **2**, it was observed that 2(e)-phenyl-*trans*-decalin 2,3-oxide[4] (**5**) underwent acid-catalyzed rearrangement to yield 2(e)-phenyl-*trans*-3-decalone (**5**). The nmr spectrum of **6** showed C**H** absorption at δ 3.61 ($W_{1/2}$ = 15 Hz) indicative of an axial orientation of the C-2 methine proton.

Utilizing this type of rearrangement, it was found that treatment of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**7**)[5] with a catalytic amount of *p*-TsOH in refluxing benzene afforded ketone **8**, which could be converted into the corresponding oxime **9**.

Attempts to reduce oxime **9** using catalytic hydrogenation, afforded only 2(e)-(3,4-dihydroxyphenyl)-*trans*-3-decalone oxime (**10**). LAH reduction of **9** yielded the desired 3(e)-amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin which was isolated as the HCl salt **11**. Removal of the benzyl ether protecting groups from **11** was achieved by hydrogenation using Pd/C to yield **2**. The nmr spectrum of **2** showed C-3 methine absorption at δ 3.22 ($W_{1/2}$ = 19 Hz) and the C-2 methine



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

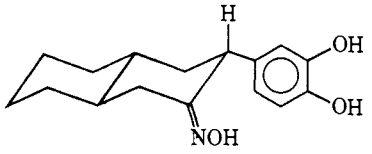
(2) Taken in part from the dissertation presented by R. T. Borchardt, April 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(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) E. E. Smissman and R. T. Borchardt, *ibid.*, **14**, 377 (1971).

absorption at δ 2.68 ($W_{1/2}$ = 20 Hz). The peak half-widths are consistent with the assigned axial orientations of the C-2 and C-3 methine protons.



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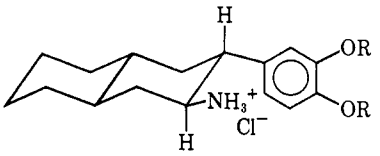

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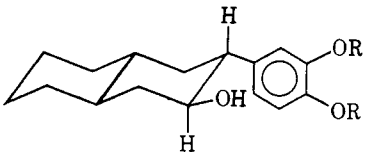
LAH reduction of ketone **8** afforded a mixture of the equatorial alcohol **12**, as the major product, and the axial alcohol **13**.



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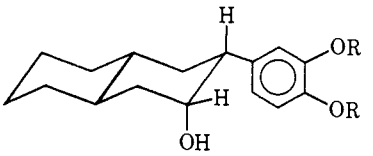
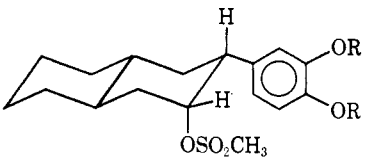


13

The axial alcohol **13** provided a further structure proof for the equatorial amine **11**. Treatment of **13** with MesCl in pyridine afforded the corresponding mesylate **14**, which on treatment with NaN_3 in DMF afforded azide **15**. The reduction of **15** using LAH yielded **11**.



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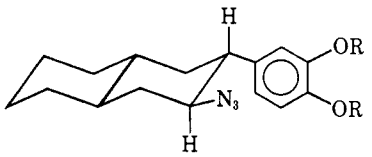


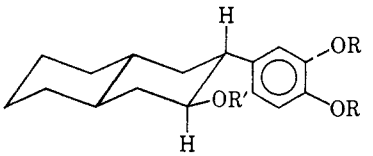
15

The equatorial alcohol **12** provided a pathway to the desired amine **1**. Treatment of **12** with *p*-TsCl in pyridine afforded the tosylate **16**. Direct displacement of the tosylate function from **16** using NH_3 at elevated temp and pressure yielded the desired axial amine **17**.

An alternate pathway to **17** involved the treatment of the tosylate **16** with NaN_3 in DMF to afford the azide **18** which was then reduced using LAH to afford the desired amine.

Removal of the benzyl ether protecting groups from **17** was achieved by hydrogenation over Pd/C to yield **1**.

The nmr spectrum of **1** showed C-3 methine absorption at δ 3.61 ($W_{1/2}$ = 8 Hz) which is in agreement with the proposed structure.



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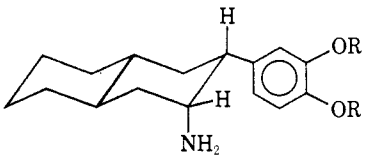

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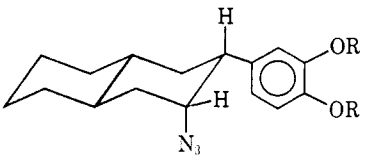

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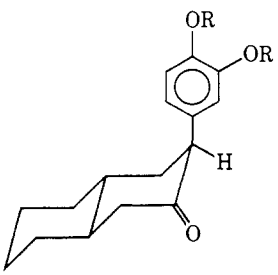
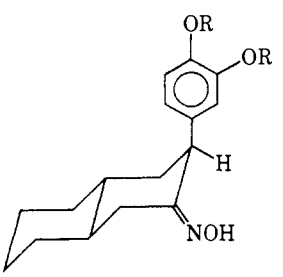
R = $CH_2C_6H_5$
R′ = *p*-$O_2SC_6H_4CH_3$

A pathway to the catecholamines **3** and **4** was found when it was observed that epoxide **7** rearranged upon warming in DMSO to afford a mixture of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**8**) and 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**19**). The axial aryl ketone **19** could be converted into quantitative yield to the corresponding equatorial aryl ketone **8** by refluxing in benzene with a catalytic amount of *p*-TsOH.



19

Treatment of ketone **19** with $HONH_2 \cdot HCl$ afforded the corresponding oxime **20**. The nmr spectrum of **20** showed 2 absorptions for the C-2 methine proton at δ 4.73 ($W_{1/2}$ = 8.5 Hz) and δ 3.72 ($W_{1/2}$ = 9 Hz). The 2 signals for the C-2 methine protons appear to be due to the presence of the syn and anti forms of the oxime **20**.



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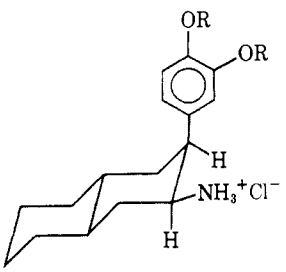

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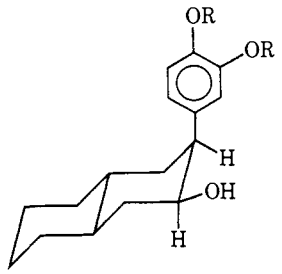
LAH reduction of oxime **20** in THF afforded the desired 3(e)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-

decalin which was isolated as the HCl salt **21**. The benzyl ether protecting groups were removed from **21** by catalytic hydrogenation to afford **4**. The nmr spectrum of **4** showed C-3 methine absorption at δ 3.35 ($W_{1/2}$ = 15 Hz) and C-2 methine absorption at δ 3.19 ($W_{1/2}$ = 8.0 Hz). The peak half-width of the C-3 methine absorption indicates an axial orientation, whereas, that of the C-2 methine absorption indicates an equatorial orientation.

Reduction of **19** using LAH afforded the desired equatorial alcohol **22**. The treatment of **22** with MesCl in pyridine afforded the corresponding mesylate **23**. The reaction of the mesylate **23** with NaN_3 in DMF produced the azide **24**.



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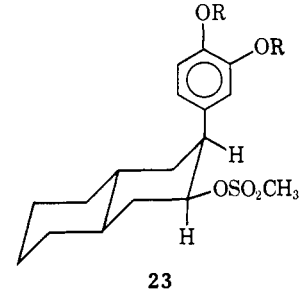
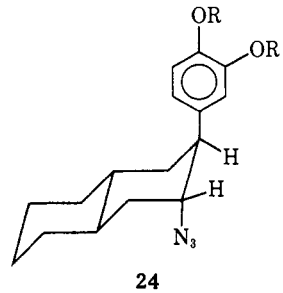


23

LAH reduction of azide **24** afforded the desired 3(a)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin which was isolated as the HCl salt **25**.

Removal of the benzyl ether protecting groups from **25** by catalytic hydrogenation afforded **3**. The nmr spectrum exhibited C-3 methine absorption at δ 3.81 ($W_{1/2}$ = 8 Hz) and C-2 methine absorption at δ 3.11 ($W_{1/2}$ = 10 Hz). The peak half-widths of the C-2 and C-3 methine absorptions are in agreement with the proposed structure.



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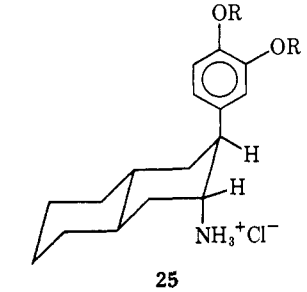

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Biological Results.—Table I lists the observed rates and relative rates of O-methylation by cathechol-*O*-methyltransferase[6] (COMT) of the α-methyldopamine analogs **1**, **2**, **3**, and **4**. Table II lists the K_m, V_{max}, and relative V_{max} values determined for the same substrates as compared to dopamine.

TABLE I

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

Compd	Conformation NH2	Conformation Aryl	nmoles of product/10 min[c]	Relative rates
1[b]	a	e	18.57	0.65
2[b]	e	e	15.49	0.55
3[b]	a	a	36.83	1.38
4[b]	e	a	2.77	0.098
Dopamine[b]			28.41	1

[a] Assay conditions, see E. E. Smissman and R. T. Borchardt, *J. Med. Chem.*, **14**, 377 (1971). [b] Hydrochloride salt. [c] Enzyme, 0.1 ml per assay.

TABLE II

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

Compd	Conformation NH2	Conformation Aryl	$K_m \times 10^{-4}$	V_{max}, nmoles of product/10 min[c,d]	Relative V_{max}
1[b]	a	e	16.8	174.2	1.27
2[b]	e	e	23.6	197.1	1.44
3[b]	a	a	8.39	190.0	1.39
4[b]	e	a	6.15	11.9	0.087
Dopamine[b]			7.77	136.9	1

[a] See footnote *a*, Table I. [b] Hydrochloride salt. [c] Enzyme, 0.1 ml per assay. [d] Correlation coefficient >0.9993.

The preliminary enzymatic data on the α-methyldopamine analogs indicate that the conformation in which the amino group and the aryl group are completely staggered best fits the active site on COMT. This is apparent from the relative rate and V_{max} data for **3**. Lesser activity as substrates for COMT was observed for **1**, **2**, and **4**, all possessing the conformation in which amino group and aryl group are gauche.

The more significant substrate specificity observed in the α-methylnorepinephrine analogs[5] relative to the α-methyldopamine analogs indicates a primary role for the β-OH group in determination of the preferred conformation for COMT activity.

Experimental Section[7]

2(e)-Phenyl-*trans*-3-decalone (**6**).—To 2(e)-phenyl-*trans*-decalin 2,3-oxide (**5**)[4] (10.0 g, 44.0 mmoles) in 100 ml of anhyd C_6H_6 was added a catalytic amount of *p*-TsOH. The mixt was refluxed for 24 hr, after which the C_6H_6 soln was washed with 5% $NaHCO_3$ soln, H_2O, and satd NaCl soln and dried ($MgSO_4$). The C_6H_6 was removed to yield a colorless oil. Crystn (hexane) afforded 6.53 g (65%) of **6**: mp 100–101°; ir ($CHCl_3$) 1712 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.41–7.00 (m, 5 H, arom), 3.61 (m, 1 H, $W_{1/2}$ = 15 Hz, C-2 C**H**). *Anal.* ($C_{16}H_{20}O$) C, H.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (**8**).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide[5] (**7**) (4.55 g, 9.65 mmoles) in 150 ml of anhyd C_6H_6 was added *p*-TsOH (0.030 g), and the mixt was heated at reflux for 18 hr. The C_6H_6 soln was washed successively with 5% $NaHCO_3$ soln, H_2O, and satd NaCl soln and dried ($MgSO_4$). The C_6H_6 was removed to yield 4.70 g of a semisolid material. Chromatography on silica gel by eluting with $CHCl_3$–hexane (3:1) afforded 2 major fractions.

Fraction A.—Recrystn (Me_2CO–hexane) afforded 2.10 g (48.0%) of **8**: mp 117–118°; ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.60–6.60 (m, 13 N, aromatic), 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 **8** which was isolated by the formation of the corresponding oxime. Recrystn ($CHCl_3$–EtOH) afforded 1.05 g (24%) of **9**, mp 204–206°.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone Oxime (**9**).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**8**) (0.50 g, 1.13 mmoles) in 50 ml of abs EtOH was added a soln of $NH_2OH \cdot HCl$ (0.500 g, 7.2 mmoles) and NaOAc (0.500 g, 6.1 mmoles) in 10 ml of H_2O. The reaction afforded 0.424 g (83%) of **9**: 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.

2(e)-(3,4-Dihydroxyphenyl)-*trans*-3-decalone Oxime (**10**).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone oxime (**9**)

(6) B. Nikadejevic, S. Senoh, J. W. Daly, and C. R. Creveling, *J. Pharmacol. Exp. Ther.*, **174**, 83 (1970).

(7) See footnote 12, paper 5, E. Smissman and R. T. Borchardt, *J. Med. Chem.*, **14**, 377 (1971).

(0.200 g, 0.44 mmole) in 150 ml of EtOAc was added 0.20 g of 10% Pd/C. Hydrogenation under conditions previously reported[5] afforded 87 mg (76.5%) of **10**: mp 206–207°; nmr (DMSO-d_6) δ 6.80–6.40 (m, 3 H, arom), 3.30 (m, 1 H, $W_{1/2}$ = 17 Hz, C-2 C**H**). *Anal.* ($C_{16}H_{21}NO_3$) C, H, N.

3(e)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin·HCl (11). A. From 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone Oxime (9).—LAH (0.500 g, 13.2 mmoles) in 50 ml of anhyd THF was heated to reflux for 2 hr. To the LAH soln was added a soln of 2(e)-(3,6-dibenzyloxyphenyl)-*trans*-3-decalone oxime (**9**) (1.50 g, 3.3 mmoles) in 75 ml of anhyd THF. The mixt was heated to reflux for 16 hr after which "wet" Et_2O followed by H_2O was added dropwise to decompose excess LAH. The H_2O layer was washed several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$). The Et_2O was removed to yield 1.45 g of a semisolid material. The crude amine was dissolved in 50 ml of Et_2O and added to a satd HCl–Et_2O soln. The resulting solid material was recovered by filtration and recrystn (EtOH–Et_2O) afforded 0.850 g (54%) of **11**: mp 267–269°; nmr ($CDCl_3$, free base) δ 7.60–6.80 (m, 13 H, arom), 5.15 (2 s, 4 H, benzylic), 2.90 (m, 1 H, $W_{1/2}$ = 16 Hz, C-3 C**H**), 2.10 (m, 1 H, $W_{1/2}$ = 19 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{36}ClNO_2$) C, H, N.

B. From 3(e)-Azido-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (15).—A soln of LAH (0.050 g, 1.32 mmoles) in 15 ml of anhyd Et_2O was refluxed for 2 hr after which **15** (0.200 g, 0.425 mmole) in 20 ml of anhyd Et_2O was added at such a rate as to maintain reflux. The soln was refluxed for 2 hr after which "wet" Et_2O followed by H_2O was added to decompose the excess LAH. The aq soln was washed several times with Et_2O, and the combined Et_2O fractions were washed with H_2O and satd NaCl soln and dried ($MgSO_4$). The solvent was removed to yield a colorless oil. The oil was dissolved in Et_2O and added to a satd HCl–Et_2O soln. The HCl salt was removed by filtration and recrystd (Et_2O–EtOH) to yield 0.162 g (81.5%) of **11**, mp 266–269°.

3(e)-Amino-2(e)-(3,4-dihyroxyphenyl)-*trans*-decalin·HCl (2).—To 3(e)-amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin·HCl (**11**) (1.10 g, 2.30 mmoles) in 35 ml of anhyd MeOH was added 250 mg of 10% Pd/C under N_2. The mixt was hydrogenated at 25° at atm pressure to afford 0.630 g (92%) of **2**: mp 272–275°; nmr (CD_3OD) δ 6.97–6.68 (m, 3 H, arom), 3.22 (m, 1 H, $W_{1/2}$ = 19 Hz, C-3 C**H**), 2.68 (m, 1 H, $W_{1/2}$ = 20 Hz, C-2 C**H**). *Anal.* ($C_{16}H_{24}ClNO_2$) C, H, N.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(e)-decalol (12) and 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(a)-decalol (13).—LAH (0.270 g, 7.2 mmoles) in 50 ml of anhyd THF was heated to reflux for 2 hr. To the LAH soln was added a soln of 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**8**) (3.00 g, 6.85 mmoles) in 50 ml of anhyd THF at such a rate as to maintain reflux. The mixt was heated to reflux for 1 hr after which "wet" C_6H_6 followed by H_2O was added dropwise to decomp excess LAH. The H_2O soln 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 was removed to yield 3.10 g of a semisolid material. Chromatography on silica gel by eluting with $CHCl_3$ afforded two cryst fractions.

Fraction A. 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(a)-decalol (13).—Recrystn ($CHCl_3$–hexane) afforded 0.205 g (8.0%) of **13**: mp 96–98°; ir (KBr) 3570, 3470 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.63–6.80 (m, 13 H, arom), 5.15 (2 s, 4 H, benzylic), 3.97 (m, 1 H, $W_{1/2}$ = 7.5 Hz, C-3 C**H**), 2.83 (m, 1 H, $W_{1/2}$ = 20 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{34}O_3$) C, H.

Fraction B. 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(e)-decalol (12).—Recrystn ($CHCl_3$–hexane) afforded 2.05 g (68%) of **12**: mp 138–139°; ir (KBr) 3580, 3460 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.60–6.85 (m, 13 **H**, arom), 5.15 (2s, 4 H, benzylic), 3.60 (m, 1 H, $W_{1/2}$ = 17.5 Hz, C-3 C**H**), 2.40 (m, 1 H, C-2 C**H**). *Anal.* ($C_{30}H_{34}O_3$) C, H.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(a)-decalol-3(a)-mesylate (14).—To 2(e)-(3,6-dibenzyloxyphenyl)-*trans*-3(a)-decalol (**13**) (0.500 g, 1.2 mmoles) dissolved in 5 ml of anhyd C_6H_5N was added MsCl (0.274 g, 2.4 mmoles) in 1 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 Et_2O and the combined Et_2O fractions were washed with H_2O and satd NaCl soln. The Et_2O fraction was dried ($MgSO_4$), and the Et_2O was removed to yield a semisolid product. Recrystn (Me_2CO–hexane) afforded 0.525 g (81%) of **14**: mp 101–103°; nmr ($CDCl_3$) δ 7.61–6.80 (m, 13 H, arom), 5.21 (s, 2 H, benzylic), 5.18 (s, 2 H, benzylic), 4.78 (m, 1 H, $W_{1/2}$ = 6 Hz, C-3 C**H**), 2.88 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 C**H**). 1.89 (s, 3 H, mesylate CH_3). *Anal.* ($C_{31}H_{36}O_5S$) C, H.

3(e)-Azido-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (15).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3(a)-decalol-3(a)-mesylate (**14**) (0.600 g, 1.15 mmoles) dissolved in 40 ml of DMF was added a soln of NaN_3 (0.374 g, 5.75 mmoles) in 4 ml of H_2O. The mixt was heated at 90–100° for 24 hr, after which the soln was cooled, and H_2O was added. The aq layer was washed 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 solvent was removed to yield a colorless oil which crystd upon standing. Recrystn (hexane) afforded 0.410 g (76.5%) of **15**: mp 100–102°; ir ($CHCl_3$) 2050 cm^{-1} (azide); nmr ($CDCl_3$) δ 8.68–6.82 (m, 13 H, arom), 5.18 (s, 2 H, benzylic), 5.12 (s, 2 H, benzylic), 3.23 (m, 1 H, $W_{1/2}$ = 20 Hz, C-3 C**H**), 2.60 (m, 1 H, C-2 C**H**). *Anal.* ($C_{30}H_{33}N_3O_2$) C, H, N.

2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(e)-decalol 3-Tosylate (16).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3(e)-decalol (**12**) (2.00 g, 4.8 mmoles) dissolved in 25 ml of anhyd C_6H_5N was added *p*-TsCl (2.00 g, 10.0 mmoles) and the mixt was allowed to stir at 25° for 14 hr. H_2O was added, and the aq layer was extd several times with C_6H_6. The combined C_6H_6 fractions were washed with 5% $NaHCO_3$ soln, satd NaCl soln, and H_2O and dried ($MgSO_4$). The C_6H_6 was removed to yield 2.50 g of a semisolid product. Recrystn ($CHCl_3$–hexane) afforded 2.05 g (72%) of **16**: mp 132–133.5°; nmr ($CDCl_3$) δ 6.45 (m, 17 H, arom), 5.09 (s, 2 H, benzylic), 4.95 (s, 2 H, benzylic), 4.40 (m, 1 H, C-3 C**H**), 2.50 (m, 1 H, C-2 CH), 2.25 (s, 3 H, aryl CH_3). *Anal.* ($C_{37}H_{40}O_5S$) C, H.

3(a)-Azido-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (18).—To 2(e)-(3,4-dibenzyloxyphenyl)-*trans* 3(e)-decalol 3-tosylate (**16**) (0.500 g, 0.84 mmole) dissolved in 40 ml of DMF was added a soln of NaN_3 (0.275 g, 4.2 mmoles) in 4 ml of H_2O. The procedure utilized was identical with that used in the preparation of **15** to yield 0.450 g of a semisolid material. Recrystn ($CHCl_3$–hexane) afforded 0.325 g (82.5%) of **18**: mp 117–118°; ir (KBr) 2080 cm^{-1} (azide); nmr ($CDCl_3$) δ 7.60–6.80 (m, 13 H, arom), 5.18 (s, 2 H, benzylic), 5.12 (s, 2 H, benzylic), 3.87 (m, 1 H, $W_{1/2}$ = 8 Hz, C-3 C**H**), 2.69 (m, 1 H, $W_{1/2}$ = 19 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{33}N_3O_2$) C, H, N.

3(a)-Amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (17). A. From 3(a)-Azido-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (18).—LAH (0.050 g, 1.32 mmoles) in 15 ml of anhyd Et_2O was heated to reflux for 2 hr. To the LAH soln was added a soln of 3(a)-azido-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (**18**) (0.200 g, 0.425 mmole) in 20 ml of anhyd Et_2O at such a rate as to maintain reflux. The mixt was heated to reflux for 2 hr after which "wet" Et_2O followed by H_2O was added dropwise to decomp excess LAH. The aq layer was washed several times with Et_2O, and the Et_2O was removed to yield a yellowish oil which crystd upon addition of hexane. Recrystn ($CHCl_3$–hexane) afforded 0.135 g (74.5%) of **17**: mp 85–87°; nmr ($CDCl_3$) δ 7.60–6.75 (m, 13 H, arom), 5.17 (s, 2 H, benzylic), 5.14 (s, 2 H, benzylic), 3.23 (m, 1 H, $W_{1/2}$ = 11 Hz, C-3 C**H**), 2.75 (m, 1 H, $W_{1/2}$ = 18 Hz, C-2 C**H**). *Anal.* ($C_{30}H_{35}NO_2$), C, H, N.

B. From 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(e)-decalol 3-Tosylate (16).—2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3(e)-decalol 3-tosylate (**16**) (0.500 g, 0.84 mmole) was treated with liq NH_3 under conditions previously reported[5] to afford 0.380 g of a yellowish oil. Chromatography on silica gel by eluting with $CHCl_3$ afforded, after recrystn ($CHCl_3$–hexane), 0.205 g (57%) of **17**, mp 85–87°.

3(a)-Amino-2(e)-(3,4-dihydroxyphenyl)-*trans*-decalin·HCl (1).—To 3(a)-amino-2(e)-(3,4-dibenzyloxyphenyl)-*trans*-decalin (**17**) (1.00 g, 2.1 mmoles) in 30 ml of anhyd MeOH was added 250 mg of 10% Pd/C under N_2. The mixt was hydrogenated at 25° and 1 atm pressure. Dry HCl was slowly bubbled into the mixt, after which the catalyst was removed by filtration, and the solvent was removed *in vacuo*. The product was crystd (EtOH–Et_2O) to yield 0.453 g (71%) of **1**: mp 274–278°; nmr (CD_3OD) δ 6.95–6.65 (m, 3 H, aromatic), 3.61 (m, 1 H, $W_{1/2}$ = 8 Hz, C-3 C**H**). *Anal.* ($C_{16}H_{24}NO_2Cl$) C, H, N.

2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (19) and 2(e)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (8).—2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-decalin 2,3-oxide (**7**) (4.50 g, 9.60 mmoles) was dissolved in 450 ml of DMSO and heated at 100° for 15 min. H_2O was added, and the H_2O layer was extd several times with C_6H_6. 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 afford 4.75 g of a semisolid product. Chromatography on silica gel by eluting with 15% EtOAc–hexane afforded 3 major fractions.

Fraction A. 2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (19).—Recrystn (Me_2CO–hexane) afforded 1.05 g (23.5%) of **19**: mp 80–83°; ir (KBr) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.55–6.79 (m, 13 H, arom), 5.14 (s, 4 H, benzylic), 3.64 (m, 1 H, $W_{1/2}$ = 7.5 Hz, C-2 CH). *Anal.* ($C_{30}H_{32}O_3$) C, H.

Fraction B. 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (8).—Recrystn (Me_2CO–hexane) afforded 1.20 g (27.2%) of **8**, mp 117–118°.

Fraction C.—Impure **8** was isolated by formation of the corresponding oxime. Recrystn ($CHCl_3$–EtOH) afforded 0.850 g of **9**, mp 205–207°.

Conversion of 2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (19) into 2(e)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (8).—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**19**) (0.100 g, 0.23 mmole) in 20 ml of anhyd C_6H_6 was added 2 mg of *p*-TsOH. The C_6H_6 soln was heated to reflux for 12 hr after which the C_6H_6 soln was washed with 5% $NaHCO_3$ soln and H_2O and dried ($MgSO_4$). The C_6H_6 was removed to afford 0.092 g of a semisolid product. Recrystn (Me_2CO–hexane) yielded 0.082 g (82%) of **8**, mp 117–118°.

2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone Oxime (20).—2(a)-(3,4-Dibenzyloxyphenyl)-*trans*-3-decalone (**19**) (0.600 g, 1.36 mmoles) in 50 ml of abs EtOH, 0.400 g of $NH_2OH \cdot HCl$, and 0.400 g of NaOAc in 10 ml of H_2O afforded 0.560 g (90.5%) of **20**: mp 119–122°; nmr ($CDCl_3$) δ 7.55–6.75 (m, 13 H, arom), 5.14 (s, 4 H, benzylic), 4.73 (m, 0.5 H, $W_{1/2}$ = 8.5 Hz, C-2 CH), 3.72 (m, 1/2 H, $W_{1/2}$ = 9 Hz, C-2 CH). *Anal.* ($C_{30}H_{33}NO_3$) C, H, N.

3(e)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin·HCl (21).—To a soln of LAH (0.170 g, 4.4 mmoles) in 25 ml of anhyd THF was added dropwise a soln of 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone oxime (**20**) (0.500 g, 1.10 mmoles) in 25 ml of anhyd THF as in the preparation of **11** to afford 0.305 g (58.5%) of **21**: mp 214–215°; nmr ($CDCl_3$, free base) δ 7.55–6.85 (m, 13 H, arom), 5.18 (2 s, 4 H, benzylic), 3.00 (m, 1 H, $W_{1/2}$ = 7.5 Hz, C-2 CH), 2.95 (m, 1 H, $W_{1/2}$ = 14 Hz, C-3 CH). *Anal.* ($C_{30}H_{36}ClNO_2$) C, H, N.

3(e)-Amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-decalin·HCl (4).—To 3(e)-amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-decalin·HCl (**21**) (0.151 g, 0.31 mmole) in 5 ml of anhyd MeOH was added 50 mg of 10% Pd/C under N_2. The mixt was hydrogenated at 25° and atm pressure to afford 77 mg (84%) of **4**: mp 285–290°; nmr (CD_3OD) δ 7.03–6.65 (m, 3 H, arom), 3.35 (m, 1 H, $W_{1/2}$ = 15 Hz, C-3 CH), 3.19 (m, 1 H, $W_{1/2}$ = 8.0 Hz, C-2 CH). *Anal.* ($C_{16}H_{24}ClNO_2$) C, H, N.

2(a)-(3,4-Dihydroxyphenyl)-*trans*-3(e)-decalol (22).—LAH (0.270 g, 7.2 mmoles) in 50 ml of anhyd Et_2O and a soln of 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3-decalone (**19**) (3.00 g, 6.85 mmoles) in 50 ml of anhyd Et_2O were allowed to react in a procedure similar to that used for **12** to yield 2.22 g (73.5%) of **22**: mp 99–100°; ir ($CHCl_3$) 3578 cm^{-1} (OH); nmr ($CDCl_3$) δ 7.66–6.80 (m, 13 H, arom), 5.17 (s, 2 H, benzylic), 5.12 (s, 2 H, benzylic), 3.85 (m, 1 H, $W_{1/2}$ = 18 Hz, C-3 CH), 3.18 (m, 1 H, $W_{1/2}$ = 10 Hz, C-2 CH). *Anal.* ($C_{30}H_{34}O_3$) C, H.

2(a)-(3,4-Dibenzyloxyphenyl-*trans*-3(e)-decalol 3(e)-Mesylate (23).—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3(e)-decalol (**22**) (1.10 g, 2.5 mmoles) in 10 ml of anhyd C_6H_5N was added MsCl (0.350 g, 3.00 mmoles) in 2 ml of anhyd C_6H_5N in a procedure similar to that for **14** to yield 1.40 g of a colorless oil: nmr ($CDCl_3$) δ 4.89 (m, 1 H, C-3 CH), 3.41 (m, 1 H, $W_{1/2}$ = 11 Hz, C-2 CH). The crude mesylate was utilized without further purification.

3(a)-Amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin·HCl (25).—To 2(a)-(3,4-dibenzyloxyphenyl)-*trans*-3(e)-decalol 3(e)-mesylate (**23**) (1.30 g, 2.4 mmoles) in 80 ml of DMF was added a soln of NaN_3 (0.325 g, 5.0 mmoles) in 10 ml of H_2O in a procedure similar to that used for **15** to yield 1.20 g of **24**: ir (neat) 2105 cm^{-1} (azide); nmr ($CDCl_3$) δ 4.04 (m, 1 H, $W_{1/2}$ = 7 Hz, C-3 CH), 2.95 (m, 1 H, $W_{1/2}$ = 9.5 Hz, C-2 CH).

A soln of LAH (0.250 g, 6.6 mmoles) in 50 ml of anhyd Et_2O and the azide **24** in 50 ml of anhyd Et_2O was treated in manner similar to that used for the preparation of **17**. Chromatography on silica gel by eluting with 5% MeOH–$CHCl_3$ afforded 0.605 g of a colorless oil. Formation of the HCl salt and recrystn (MeOH–Et_2O) yielded 0.50 g (40%) of **25**: mp 147–148°; nmr ($CDCl_3$, free base) δ 7.55–6.80 (m, 13 H, aromatic), 5.13 (s, 2 H, benzylic), 5.10 (s, 2 H, benzylic), 3.42 (m, 1 H, $W_{1/2}$ = 9 Hz, C-3 CH), 2.78 (m, 1 H, $W_{1/2}$ = 11 Hz, C-2 CH). *Anal.* ($C_{30}H_{36}ClNO_2$) C, H, N.

3(a)-Amino-2(a)-(3,4-dihydroxyphenyl)-*trans*-decalin·HCl (3).—To 3(a)-amino-2(a)-(3,4-dibenzyloxyphenyl)-*trans*-decalin·HCl (**25**) (0.240 g, 0.50 mmole) in 15 ml of anhyd MeOH was added 60 mg of 30% Pd/C under N_2. Hydrogenation under conditions previously reported[5] afforded 0.124 g (83%) of **3**: mp 136–139°; nmr (CD_3OD) δ 7.15–6.65 (m, 3 H, aromatic), 3.81 (m, 1 H, $W_{1/2}$ = 8 Hz, C-3 CH), 3.11 (m, 1 H, $W_{1/2}$ = 10 Hz, C-2 CH). *Anal.* ($C_{16}H_{24}ClNO_2$) C, H, N.

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