layer was dried, the solvent was evaporated, and the residue was purified by crystallization. Ir spectra were as expected.

6- and 7-Substituted 3-Carbamoyl-1H-3,4-dihydro-2,3-benzoxazines (IVc, Vf, VIIc). General Procedure. 6-Chloro-3-carbamoyl-1H-3,4-dihydro-2,3-benzoxazine (VIIc).—To a stirred suspension of NaCNO (1.56 g, 24 mmoles) in 75 ml of anhydrous toluene, 23 mmoles of dry HCl in toluene was added dropwise at −10°. After 2 hr of stirring, a solution of VIIa (2.7 g, 16 mmoles) in 40 ml of anhydrous toluene was added and the temperature was kept at −10° for 3 hr, then at 0° overnight. The precipitate was collected, thoroughly washed (PhMe, H_2O), and crystallized (EtOH). Ir absorption bands were as expected.

6-Nitro-3-phenylcarbamyl-1H-3,4-dihydro-2,3-benzoxazine (Vf).—To a solution of Va (0.9 g, 5 mmoles) in 40 ml of anhydrous C_6H_6, phenyl isocyanate (0.65 g, 5 mmoles) was added dropwise. The mixture was allowed to stand 3 hr at room temperature, and the precipitate was collected and recrystallized (EtOH). Absorption bands of spectra (ir) were as expected.

6- and 7-Chloro-3-guanyl-1H-3,4-dihydro-2,3-benzoxazines (IVe, VIIe). General Procedure. 7-Chloro-3-guanyl-1H-3,4-dihydro-2,3-benzoxazine Sulfate (IVe).—A suspension of IVa·HCl (1.5 g, 7.25 mmoles) and cyanamide (0.31 g, 7.4 mmoles) in 30 ml of anhydrous C_6H_6 was refluxed 1 hr and the mixture was allowed to stand overnight at room temperature. The precipitate was collected (1.75 g of IVe·HCl, mp 228–230°), dissolved in EtOH (25 ml), and transformed into the corresponding sulfate by adding 0.75 ml of concentrated H_2SO_4 and 25 ml of Et_2O. Absorption bands (ir) were as expected.

6- and 7-Substituted 3-[2-(4-Pyridylethyl)]-1H-3,4-dihydro-2,3-benzoxazines (IIj, VIIh). General Procedure. 7-Nitro-3-[2-(4-pyridylethyl)]-1H-3,4-dihydro-2,3-benzoxazine Hydrochloride (IIj).—To a stirred solution of 10 mmoles of dry HCl in 45 ml of EtOH, IIa (1.8 g, 10 mmoles) was added with stirring. After 10 min at ambient temperature, 4-vinylpyridine (1.16 g, 11 mmoles) was added and the mixture was refluxed for 2 hr. After cooling overnight, the precipitate was collected and recrystallized (EtOH). Ir absorption bands were as expected.

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The Absolute Configurations of the Pheniramines,[1a] Methyl Phenidates,[1b] and Pipradrols[1c,2]

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Absolute configurations of the 16 optical isomers of seven[1] structurally related, title compounds of biological interest were determined. The pheniramines were converted to a methyl phenidate in which the relative configurations of the two asymmetric centers was established. The endocyclic center of asymmetry introduced in the process was maintained intact while the asymmetry of the exocyclic center was destroyed in the conversion to a pipradrol derivative. This was related to pipradrol by an *aufbau* sequence starting with (*R*)-(+)-piperidine-2-carboxylic acid. The absolute configurations of desoxypipradrol and thiopipradrol were established by Birch reduction and by rotatory dispersion, respectively. The antihistaminically more active acid maleates of **1a** and **1b** are stereochemically superimposable upon **1c** and all have the (*S*) configuration. The analeptically more active hydrochlorides (**25, 19, 26**) of *threo*-methyl phenidate, pipradrol, and thiopipradrol are stereochemically superimposable upon **22**. These have the (2*R*:2'*R*), (*R*), (*S*), and (*R*) configurations, respectively, but are not stereochemically superimposable upon the analeptically more active (+) acid sulfate of amphetamine.

Knowledge of the absolute configurations of biologically active compounds provides a valuable probe for investigating their modes of action and their interactions with hypothetical receptors.[4] This and the facts that the absolute configurations of the pheniramines (**1**), methyl phenidates (**9, 25**), and pipradrols (**19, 22, 26**) have not been reported, that their optical isomers exhibit significant differences in activity,[5–8] and that speculation regarding the absolute configuration of **1a** and its necessarily complimentary receptor exists in the literature[9] prompted this study. Since the pheniramines, methyl phenidates, and pipradrols are structurally related, 2-substituted, six-membered, nitrogen heterocycles with an asymmetric center adjoining the heterocyclic ring, it was possible to develop and to exploit a single sequence of reactions leading to the determination of absolute configurations of the sixteen optical isomers of the seven entities (**1a–c, 19, 22, 25, 26**) of biological interest.

The salient features of the sequence are the con-

(1) (a) The antihistaminic 3-(*p*-chlorophenyl)-, 3-(*p*-bromophenyl)-, and 3-phenyl-3-(2-pyridyl)-1-dimethylaminopropanes; (b) the analeptic methyl *threo*-2-phenyl-2-(2-piperidyl)acetates; (c) the analeptic α-(2-piperidyl)-benzhydrol and the desoxy and 1,4-thiomorpholinyl analogs.

(2) Partial support was provided by National Institutes of Health (Grant No. NB-03593), U. S. Public Health Service. The authors gratefully acknowledge partial financial support from Schering and Ciba Laboratories and gifts of generous samples of the (+) acid maleate of chlorpheniramine supplied by Drs. H. Wolkoff, B. Jaini, and H. Leitzow, Schering Laboratories, of the (+) acid maleate of brompheniramine supplied by Dr. W. Schlesinger, White Laboratories, and Dr. H. Wolkoff, Schering Laboratories, of (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide supplied by Dr. L. Lachman and Mr. J. Cooper, Ciba Laboratories, and of the antipodal hydrochlorides of thiopipradrol made available by Dr. B. Belleau, University of Ottawa, and Dr. H. Leo Dickison, Bristol Laboratories.

(3) (a) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967. Abstracted from the M.S. and Ph.D. theses of A. S., Columbia University, 1965 and 1968, respectively. Recipient, Iranian Government Scholarship, 1963–1967. Regional and National First Prize Winner Lunsford-Richardson Awards, 1967, Graduate Competition. (b) Author to whom inquiries should be addressed.

(4) P. S. Portoghese, *J. Pharm. Sci.*, **55**, 865 (1966); *J. Med. Chem.*, **8**, 609 (1965); B. Belleau and G. Lacasse, *ibid.*, **7**, 768 (1964); B. Belleau, *ibid.*, **7**, 776 (1964); B. Belleau and J. Puranen, *ibid.*, **6**, 325 (1963).

(5) (a) R. T. Brittain, P. F. D'Arcy, and J. H. Hunt, *Nature*, **183**, 734 (1959); (b) F. E. Roth and W. M. Govier, *J. Pharmacol. Exp. Ther.*, **124**, 347 (1958); (c) F. E. Roth, *Chemotherapia*, **3**, 120 (1961).

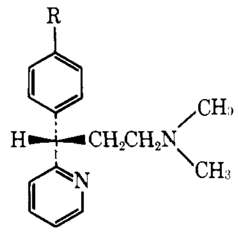
(6) R. Rometsch, U. S. Patent 2,838,519 (1958).

(7) B. Belleau, *J. Med. Chem.*, **2**, 553 (1960).

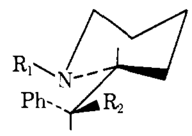
(8) P. Portoghese, T. L. Pazdernik, W. L. Kuhn, G. Hite, and A. Shafi'ee, *ibid.*, **11**, 12 (1968).

(9) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1964, p 373.

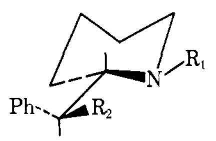
version of the pheniramines (**1**) to a methyl phenidate (**9**) in which the relative configurations of the two asymmetric centers were known.[6,10] Destruction of the



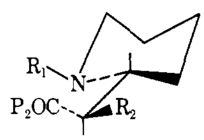
(+)-(S)
Ia, R = Cl
b, R = Br
c, R = H



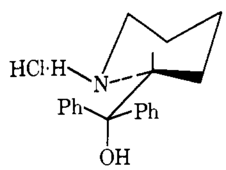
2, R_1 = H; R_2 = $CH_2CH_2NMe_2$
3a, R_1 = PhCO; R_2 = $CH_2CH_2NMe_2$
4a, R_1 = PhCO; R_2 = $CH{=}CH_2$
6a, R_1 = PhCO; R_2 = CH_2CH_3
5, R_1 = PhCO; R_2 = COOH
7, R_1 = H·HCl; R_2 = COOH
8, R_1 = H; R_2 = $CONH_2$
9, R_1 = H·HCl; R_2 = COOMe
10, R_1 = PhCO; R_2 = COOMe
11, R_1 = $PhSO_2$; R_2 = COOMe
12, R_1 = $PhSO_2$; R_2 = CH_2OH
13, R_1 = $PhSO_2$; R_2 = CH_2Cl



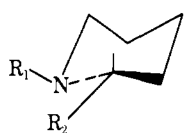
3b
4b
6b



(+)-(2R:2'R)
23, R_1 = H; R_2 = NH_2
24, R_1 = H·HCl; R_2 = OH
25, R_1 = H·HCl; R_2 = OMe



26 (−)-(S)



14, R_1 = $PhSO_2$; R_2 = PhC(=CH_2)
15, R_1 = $PhSO_2$; R_2 = PhCO
16, R_1 = $PhSO_2$; R_2 = Ph_2COH
17, R_1 = H; R_2 = COOH (+)-(R)
18, R_1 = H; R_2 = COOMe
19, R_1 = H·HCl; R_2 = Ph_2COH (−)-(R)
20, R_1 = $PhSO_2$; R_2 = COOH
21, R_1 = $PhSO_2$; R_2 = COOMe
22, R_1 = H·HCl; R_2 = Ph_2CH (−)-(R)

asymmetry of the exocyclic center led to a pipradrol derivative (**16**) which was elaborated from (R)-(+)-piperidine-2-carboxylic acid (**17**).[11]

Dehalogenation of **1a**, **1b**, or their acid maleates afforded **1c** identified as the (+)-monohydrobromide. Thus, the (+)-pheniramines are stereochemically superimposable.

Wolkoff[12] had observed a slow base-catalyzed racemization of **1a** indicating that the methine hydrogen is activated by the two aromatic rings. Nevertheless, Hofmann elimination of **1c** was tried. This afforded racemic products. Accordingly, reductions of **1a–c** were undertaken. This gave three mixtures of diastereoisomeric, liquid amines (**2**). Under Schotten–Baumann conditions, the three reaction mixtures gave mixtures of diastereoisomeric aminobenzamides (**3**). Fractional crystallization of each mixture afforded a solid basic amide assigned the *erythro* configuration (**3a**) and a residual oil containing the endocyclic epimer (**3b**).

Assignment of the *erythro* stereochemistry to **3a** is justified since it affords **5** which is already designated[6,10] as *erythro*. Throughout this work the assignment of *erythro* and *threo* stereochemistry is arbitrarily based upon the stereochemical relationships of the C_2 and $C_{2'}$ methine protons and the C_2 phenyl and $C_{2'}$ methylene moieties. This is in agreement with established[6,10] stereochemical assignments for **8** and **23**. All stereochemical designations are based on this chemical lineage since they are consistent and unique to the sequence of reactions described even through it would be difficult to argue against designation of **3a**, **4a**, and **6a** as *threo* structures. No current method of assignment is without ambiguity.

Hofmann elimination of **3a** and **3b** afforded (+)-methines assigned the structures **4a** and **4b**, respectively. The reduction of **4a** and **4b** to (+)-**6a** and (+)-**6b**, respectively, and the nmr spectra of these are in accord with the structural assignments.

The initial low yield (15%) of **4a** opened the question of possible epimerization of the exocyclic center in the elimination sequence. The methine from **3a** must be designated as one of two possible diastereoisomers, (+)-*erythro* or (+)-*threo*, one of which might have arisen by exocyclic epimerization. The isolation of this epimer, possibly in the presence of a larger quantity of the exocyclic epimer (and perhaps some of the conjugated olefin), might have been fortuitous. Thus, it was necessary to prove that the stereochemistry of **4a** is the same about the exocyclic center as that of **3a**, **4b**, and **1**.

Since **4a** and **4b** are clearly epimeric at the endocyclic center and are not antipodes, the stereochemistry of the exocyclic center in **4a** and **4b** must be the same. In investigating a facile route to the N-benzoyl analog of **15**, attempts to epimerize **4a** in acid or base failed. In both cases the nmr spectra and the specific rotations of the neutral product were the same as that of the starting material. This indicates that exocyclic epimerization is unlikely during or following the elimination sequence. Hofmann elimination of the quaternary deuterioxide of **3a** afforded **4a** containing five atoms of deuterium in excess of the normal isotopic abundance per 100 molecules of **4a**. Deuterium exchange into the α and γ positions[13,14] of the quaternary deuterioxide of **3a** or the 1 and 3 positions of the methine **4** is independently verifiable by proceeding one step further along the selected degradative pathway. Thus, ozonolysis of deuterio-**4a** afforded **5**. This step resulted in the loss of one of the carbon atoms in question while the second remained chemically and sterically intact. The acid **5** contained less than one atom of deuterium in excess of the normal isotopic abundance per 100 molecules of **5**. Thus, epimerization was negligible and **1**, **3a**, **4a**, and **4b** must have the same stereochemistry about the exocyclic center.

That **3a**, **4a**, and **5** have the *erythro* stereochemistry was shown by hydrolysis of **5** to **7**, identical in all respects with that prepared from the known[6,10] amide

(10) I. Weisz and A. Dudas, *Acta Pharm. Hung.*, **31** (B Suppl.), 116 (1961); *Chem. Abstr.*, **57**, 11154 (1962); I. Weisz and A. Dudas, *Monatsh.*, **91**, 840 (1960).

(11) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950).

(12) H. Wolkoff, Schering Corp., personal communication, 1963.

(13) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **77**, 521 (1955).

(14) J. Shiner and M. L. Smith, *ibid.*, **80**, 4095 (1958).

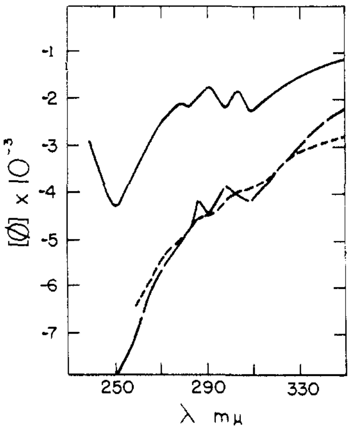


Figure 1.—The rotatory dispersion curves of (*R*)-(+)-desoxypipradrol (c 4.86 × 10^{-4} mole/100 ml) (———), (*R*)-(+)-pipradrol (c 4.05 × 10^{-4} mole/100 ml) (— —), and (*S*)-(+)-thiopipradrol (c 3.96 × 10^{-4} mole/100 ml) (- - - -) in 0.11 *N* hydrochloric acid.

(**8**). Epimerization did not occur in this step since the product of the sequence, **8** → **7** → **9** → **10** → **5**, was identical in all respects with that prepared from **1**.

The degradation to the pipradrol series began with the conversion of the free amino ester from **9** to the benzenesulfonamide (**11**). The choice of a suitable blocking group and its interposition at this point in the sequence was mandated by the nature of subsequent reactions in the sequence leading to **15**. Reduction (LAH) of **11** afforded the corresponding alcohol (**12**). The attempt to prepare the tosylate, or the corresponding olefin under more vigorous conditions, afforded instead the alkyl halide **13**. Precedent exists for similar transformations.[15]

Although treatment of **13** with refluxing NaOMe (MeOH) failed to afford **14**, treatment with KNH_2 (NH_3) was successful. Ozonolysis of **14** afforded the ketone **15**. This was converted to **16**, identical in all respects with that obtained in the following *aufbau* sequence from (*R*)-(+)-piperidine-2-carboxylic[11] acid (**17**).

Following its synthesis from picolinic acid by catalytic reduction and resolution, **17** was esterified. The crude, amino ester (**18**) afforded (*R*)-(+)-α-(2-piperidyl)-benzhydrol, the more active[8] CNS stimulant antipode, which forms a (−)-hydrochloride (**19**).[16] The base from **19** yielded **16**, which was also identical in all respects with that prepared by the sequence **17** → **20** → **21** → **16**.

The base from **19** was reduced under Birch conditions to afford (*R*)-(+)-2-benzhydrylpiperidine, isolated as the (−)-hydrochloride salt (**22**). Since **8** has the (*R*) configuration (*cf.* **17**) at the endocyclic center, and since **8** is known[6,10] to have the *erythro* stereochemistry, it must have the (*S*) configuration at the exocyclic center.

Rometsch[6] had epimerized **8** to **23** which, upon hydrolysis followed by esterification, was converted to **24** and **25**. Thus, the absolute configuration of **25**, the more active[6] CNS stimulant antipode, is (*2R*:*2'R*).

The rotatory dispersion curves[17] of **19**, **22**, and **26** are shown in Figure 1. The trough at 240 mμ in the curve of **22** was not fully accessible in the cases of **19** and **26**. The anomalous dispersion undoubtedly arises from an optically active transition of the aromatic system. Except for the diminished fine structure in the curve of **26**, the positions of the peaks, troughs, and inflections are the same and the general character of the cruves is similar. This justifies the conclusion that the three are stereochemically superimposable, although the required stereostructure for **26** has the (*S*) notation rather than the (*R*) notation required for **19** and **22**.[18] Thus, the more active[7] CNS stimulant (+)-antipode of thiopipradrol also has the (*S*) configuration since it is obtained from **26** (*cf.* Figure 1).

The more active CNS stimulant antipodes, **19**, **25**, and **26**, are not superimposable upon the more active[19] CNS stimulant (*S*)-(+)-antipode[20] of amphetamine sulfate. The significance of this is discussed elsewhere.[5]

The absolute configuration of the antihistaminically more active[5] acid maleates of **1a** and **1b** is (*S*) and not (*R*) as speculated by Barlow.[9] The significance of this has also been discussed elsewhere.[21]

Experimental Section[17,22]

(+)-3-Phenyl-3-(2-pyridyl)-1-dimethylaminopropane (1c).—Reduction (0.2 g of 10% Pd-C, 20°, 4.2 kg/cm², 200 ml of MeOH) of 32 g of (+)-3-(*p*-bromophenyl)-3-(2-pyridyl)-1-dimethylaminopropane (**1b**) obtained from its hydrogen maleate, $[\alpha]^{25}D$ +34 ± 2° (c 1.00, DMF) [lit.[23] $[\alpha]^{25}D$ +34.4° (c 1.00, DMF)], was continued until absorption of H_2 ceased. The crystals which formed on standing (4°) were redissolved by heating. The Pd-C was removed and the filtrate was concentrated and diluted (Et_2O) to give 24.1 g (80%) of **1c**·HBr, mp 176–177°, $[\alpha]^{24}D$ +31 ± 1° (c 2.04, H_2O). *Anal.* ($C_{16}H_{21}N_2Br$) C, H, N. This afforded **1c**, $[\alpha]^{29}D$ +37 ± 2° (c 9.54, EtOH), bp 116–117° (0.4 mm). Reduction of (+)-3-(*p*-chlorophenyl-3-(2-pyridyl)-1-dimethylaminopropane (**1a**) obtained from its hydrogen maleate, $[\alpha]^{26}D$ +20 ± 2° (c 2.00, H_2O) (lit.[5a] $[\alpha]^{20}D$ +23.5°), was slower than that for **1b**. If the product contained Cl (Na fusion) it was recycled to give **1c**, $[\alpha]^{29}D$ +30 ± 2° (c 10.20, EtOH), bp

(15) S. G. Levine, N. H. Eudy, and C. F. Leffler, *J. Org. Chem.*, **31**, 3995 (1966); J. H. Brewster and C. J. Ciotti, Jr., *J. Amer. Chem. Soc.*, **77**, 6214 (1955).

(16) Shortly after completion of this work we were advised by Dr. P. Portoghese of the University of Minnesota that he and Mr. T. Pazdernik had presented this portion of the *aufbau* sequence at the Medicinal Chemistry Meetings in Miniature at the University of Kansas (MIKI) in the spring of 1966; *cf.* ref 8.

(17) We wish to express our appreciation to Dr. P. Portoghese of the University of Minnesota for the rotatory dispersion curves, data for which will be presented in a forthcoming paper.

(18) The ultimate test for identical configurational requirements of receptors rests upon stereochemical superimposability about the asymmetric center. This does not necessarily lead to identical configurational notations in the (*R*) and (*S*) system which is based upon atomic priorities.

(19) G. A. Alles, *J. Pharmacol. Exp. Ther.*, **1**, 129 (1930); J. W. Schulte, E. C. Reif, J. A. Bacher, Jr., W. S. Lawrence, and M. L. Tainter, *ibid.*, **71**, 62 (1941).

(20) H. Phillips, *J. Chem. Soc.*, T44 (1923), and papers in this series; P. A. Levene and A. Walti, *J. Biol. Chem.*, **90**, 81 (1931); A. W. Schrecker, *J. Org. Chem.*, **22**, 33 (1957); P. Karrer and K. Erhardt, *Helv. Chim. Acta*, **34**, 2202 (1951).

(21) G. Hite and A. Shafi'ee, *J. Pharm. Sci.*, **56**, 1041 (1967).

(22) Melting points were determined with a Thomas–Hoover Unimelt apparatus or Kofler block and are uncorrected. The samples were placed in the silicone bath or on the block 10° below the reported melting point and heated at a rate of 2°/min. Boiling points are uncorrected. Elemental and isotopic analyses were performed by Drs. Weiler and Strauss, Oxford, England, or by Schwarzkopf Microanalytical Laboratories, New York, N. Y. Specific rotations were determined with a Zeiss 0.01° polarimeter in a 1-dm tube. Infrared spectra were recorded on a Perkin-Elmer Model 421 double-grating spectrophotometer. The nmr spectra were recorded on a Varian Model A-60A spectrometer as (5%) (w/v) solutions with tetramethylsilane as an internal reference standard. Solvents were removed *in vacuo*. Extracts were dried over Na_2CO_3. All analyses are within ±0.4% of the theoretical values.

(23) W. Schlesinger, White Laboratories, personal communication, 1962.

127–128° (1.0 mm). The HBr salt melted at 176–177°, mmp (with that obtained from **1b**) 176–177°. The hydrogen maleates of **1a** and **1b** also dehalogenate under these conditions to give **1c**.

Hofmann Elimination on 1c.—To 4.8 g of **1c** dissolved in 200 ml of petroleum ether (bp 30–60°) was added 3.1 g of MeI. The product, 6.23 g (75%), dissolved (H_2O) and was treated with fresh $Ag(OH)_2$ from 8.5 g of $AgNO_3$. When the supernatant gave no I^- test the solid was removed and the filtrate was concentrated to a syrup. This was heated at 0.5 mm. The distillate was redistilled to give 1.96 g (50%) of a (±) oil, bp 91–94° (0.5 mm). *Anal.* ($C_{14}H_{13}N$) C, H, N. The distillate of a second reaction, 1.67 g, was dissolved (EtOH, 10 ml) and treated with O_3 at −75°. The reaction mixture was flushed (N_2) and 0.42 g of $NaBH_4$ was added. After 12 hr the mixture was acidified (HCl, pH 5–6) and the EtOH was removed. The aqueous was made basic (Na_2CO_3) and extracted (petroleum ether). The extract was dried, decolorized, filtered, concentrated, and cooled to give 40 mg of a (±)-phenyl-2-pyridylcarbinol: mp 76–77°; ir (film), 3400 and 3618 cm^{-1} (free and bonded OH); HCl salt, mp 181–182° (lit.[24] mp 76–78 and 182–184°). The petroleum ether soluble oil, largely (±)-2-phenyl-2-(2-pyridyl)ethane, afforded 160 mg of picrate (acetone), mp 169–171° (lit.[25] mp 169°). Precedent exists for the reduction to the ethane derivative.[26]

(+)-*erythro*- **and** (+)-*threo*-**3-Phenyl-3-[2-(1-benzoyl)piperidyl]-1-dimethylaminopropane (3a and 3b).**—A solution of 39.1 g of **1a** hydrogen maleate was reduced (0.4 g of PtO_2, 18°, 3.5 kg/cm², 100 ml of H_2O). If the absorption of H_2 was incomplete, fresh PtO_2 was added and the reaction was continued until absorption of H_2 ceased. The Pt was removed and the filtrate was made alkaline (Na_2CO_3). The amine was extracted (petroleum ether) and the solvent was dried, filtered, and removed to give a (+) oil (EtOH). This was recycled (0.2 g of 10% Pd–C, 20°, 4.2 kg/cm²) if it contained Cl (Na fusion). The product (**2**) weighed 23 g (91%), bp 91–93° (0.1 mm). *Anal.* ($C_{16}H_{26}N_2$) C, H, N. A (+) oil was also obtained from **1b** hydrogen maleate and the amines **1a–c**. The (+) oils from **1a**, **1b**, and **1c** were treated with various acids to effect separation of the diastereoisomeric amines, but to no avail. To 20 g of each of the (+) oils obtained from **1a–c** was added 200 ml of 10% NaOH and 35.2 g (0.5 mole) of C_6H_5COCl. After 6 hr the mixtures were extracted ($CHCl_3$). The $CHCl_3$ was dried, filtered, and removed. Each of the residues was crystallized (Et_2O) to give 10 g (35% average yield) of **3a**: mp 134–136°, $[\alpha]^{30}D$ +50.5 ± 0.5° (*c* 6.95, EtOH). *Anal.* ($C_{23}H_{30}N_2O_3$) C, H, N. The combined mother liquors afforded small additional quantities of **3a** on standing (4°) for several months. The residual Et_2O-soluble (+) oil eventually solidified (low melting point) when the Et_2O had evaporated. This material is assigned the structure **3b**, the endocyclic epimer of **3a**.

(+)-*erythro*- **and** (+)-*threo*-**2-Phenyl-2-[2-(1-benzoyl)piperidyl]-1-propene (4a and 4b).**—To a solution of 11.68 g of **3a** in 100 ml of C_6H_6 was added 9.37 g of MeI. After 12 hr the crystals were washed (C_6H_6), dried *in vacuo*, and dissolved (D_2O, 99.9 atom % excess of D). To this was added $Ag(OD)_2$ prepared as follows. To 100 ml of absolute MeOH was added 8.0 g of clean Na. Upon completion of the reaction, the MeOH was removed and was replaced with D_2O. The solution was boiled to remove MeOH and was added to a solution of 28.0 g of anhydrous $AgNO_3$ in D_2O. The precipitate was washed (D_2O) until the filtrate was free of NO_3^- and was only slightly basic. This was then added to the solution of the quaternary iodide. The mixture was stirred until the supernatant gave no I^- test. The solid was removed and the filtrate was washed (D_2O) until the washings were only slightly basic. The filtrate and washings were combined and concentrated to a syrup which was boiled in 150 ml of anhydrous C_6H_6. After the residue dissolved and the vapors were neutral (moist litmus paper) the C_6H_6 was removed. The residue was crystallized (Et_2O) to give 5.2 g (52%) of **4a**: mp 125–126°; $[\alpha]^{26}D$ +121 ± 1° (*c* 4.66 CCl_4); nmr ($CDCl_3$), δ 7.5–6.5 (m, 10, C_6H_5CO and C_6H_5C–), 6.4–5.6 (m, 1, CH=C), 5.5–4.9 (m, 3, C=CH_2 and PhCHC=C), 4.1–2.6 (m, 3, $CHNCH_2$), 2.2–1.0 ppm (m, 6, $(CH_2)_3$). *Anal.* ($C_{21}H_{23}NO$) C, H, N. The atom per cent excess of D, found to be 0.218, corresponds to 5 atoms of D/100 moles of **4a**. Hofmann degradation of **3b** afforded a product assigned the structure **4b**: mp 171.5–173.5°; $[\alpha]^{26}D$ +92 ± 1° (*c* 2.07, CCl_4); nmr ($CDCl_3$), δ 7.5–6.5 (m, 10, C_6H_5CO and C_6H_5C), 6.4–5.6 (m, 1, CH=C), 5.4–4.9 (m, 3, C=CH_2 and PhCHC=C), 4.1–2.6 (m, 3, CHN-CH_2), 2.0–1.0 ppm (m, 6, $(CH_2)_3$). *Anal.* ($C_{21}H_{23}NO$) C, H, N. In earlier attempts at the elimination, the quaternary hydroxide of **3a** was boiled in Et_2O (4–5 days). This afforded a 15% yield of **4a**. Reduction (0.2 g of 10% Pd–C, 20°, 1.05 kg/cm², 10 ml of MeOH) of 61 mg of **4a** afforded a quantitative uptake of H_2. Removal of Pd–C, evaporation of the MeOH, and crystallization of the residue (Et_2O–petroleum ether) afforded 50 mg (80%) of **6a**: mp 115–116°; $[\alpha]^{27}D$ +40.5 ± 0.5° (*c* 2.61, EtOH); nmr ($CDCl_3$), δ 7.5–6.5 (m, 10, C_6H_5CO and C_6H_5C), 0.75 (t, 3, CCH_3), 3.6–1.0 ppm (m, 12). *Anal.* ($C_{21}H_{25}NO$) C, H, N. In like manner, **4b** afforded **6b**, mp 123–125°, $[\alpha]^{26}D$ +79.2 ± 0.5° (*c* 1.94, EtOH). *Anal.* ($C_{21}H_{25}NO$) C, H, N.

(−)-*erythro*-**2-Phenyl-2-[2-(1-benzoyl)piperidyl]acetic Acid (5).**—O_3 was passed through a solution of 4.65 g of **4a** in CCl_4 for 2 hr. The CCl_4 was decanted from the gummy residue which was treated with 100 ml of H_2O_2 (2%) and stirred for 6 hr. The H_2O was decanted and the residue was dried *in vacuo*. The residue obtained by evaporation of the CCl_4 was treated in the same manner and the oxidized products were combined and treated with excess $NaHCO_3$. The aqueous was extracted ($CHCl_3$) and acidified (HCl). The extract ($CHCl_3$) of the acid aqueous was dried, filtered, and evaporated to give a residue. This was crystallized (EtOH–H_2O) and recrystallized (EtOAc) to give 1.7 g (35%) of **5**, mp 221–222°, $[\alpha]^{27}D$ −51 ± 1° (*c* 4.71, EtOH). *Anal.* ($C_{20}H_{21}NO_3$) C, H, N. The atom per cent excess of D, found to be 0.053, corresponds to less than 1 atom of D/100 moles of **5**. Under the mild conditions of the work-up, it is unlikely that D was washed out of the 2 position of the acid in view of the vigorous conditions known to be required to effect epimerization.[6]

(−)-*erythro*-**2-Phenyl-2-(2-piperidyl)acetic Acid Hydrochloride (7) from 5.**—A suspension of 300 mg of **5** in 20 ml of 12 *N* HCl was allowed to reflux for 48 hr. After cooling and removing the starting material, the filtrate was evaporated leaving a solid which was crystallized (EtOH–Et_2O) to give 153 mg (63%) of **7**, mp 233–235°, $[\alpha]^{26}D$ −84 ± 2° (*c* 1.00, H_2O). *Anal.* ($C_{13}H_{18}ClNO_2$) C, H, N.

(−)-*erythro*-**2-Phenyl-2-(2-piperidyl)acetamide (8)** was prepared as described in the literature,[6] from (±)-*erythro*-2-phenyl-2-(2-piperidyl)acetamide, mp 168–169°, $[\alpha]^{26}D$ −64 ± 2° (*c* 2.00, 6:4 EtOH–H_2O) [lit.[6] mp 162–163°, $[\alpha]^{26}D$ −68° (*c* 1.00, 6:4 EtOH–H_2O)].

Methyl (−)-*erythro*-**2-Phenyl-2-[2-(1-benzoyl)piperidyl]acetate (10).**—For 4 hr, a stream of HCl was passed into a suspension of 1.78 g of **7** in 10 ml of boiling MeOH. After 10 hr the MeOH and HCl were removed and the residue was dissolved (H_2O). This (+) solution was made basic (NaOH) and extracted (Et_2O). The Et_2O was dried, filtered, and removed to give an oil which was treated with 1.58 g (7.0 mmoles) of $(C_6H_5CO)_2O$ in 90 ml of dry C_6H_6. After refluxing overnight the mixture was washed ($NaHCO_3$, dilute HCl). The C_6H_6 was dried, filtered, and removed. Crystallization of the residue (EtOAc) afforded 1.0 g (42%) of **10**, mp 125–126°, $[\alpha]^{27}D$ −63 ± 1° (*c* 2.36, EtOH). *Anal.* ($C_{21}H_{23}NO_3$) C, H, N.

(−)-*erythro*-**2-Phenyl-2-[2-(1-benzoyl)piperidyl]acetic Acid (5) from 10.**—To 674 mg of **10** in 20 ml of boiling 60% EtOH–H_2O, was added 5% NaOH at a rate sufficient to maintain the solution basic to phenolphthalein. When the color persisted for 30 min the EtOH was removed. The solution was washed ($CHCl_3$) and acidified (HCl). Following extraction ($CHCl_3$) the the $CHCl_3$ was dried, filtered, and removed. Crystallization of the residue (EtOAc) afforded 520 mg (80%) of **5**, mp 219–220°, $[\alpha]^{26}D$ −50 ± 1° (*c* 2.08, EtOH), mmp (with that prepared from **4a**) 219–221°.

(−)-*erythro*-**2-Phenyl-2-(2-piperidyl)acetic Acid Hydrochloride (7) from 8.**—To 17.0 g of **8** was added 75 ml of 12 *N* HCl. The mixture was boiled for 9 hr. The crystals were harvested on cooling. Recrystallization (EtOH–Et_2O) afforded 16.7 g (84%) of **7**, mp 233–235°, $[\alpha]^{26}D$ −81 ± 2° (*c* 1.00, H_2O).

Methyl (−)-*erythro*-**2-Phenyl-2-[2-(1-benzenesulfonyl)piperidyl]acetate (11).**—For 4 hr, HCl was passed into a suspension of 15.0 g of **7** in 75 ml of boiling dry MeOH. The MeOH and HCl were removed and the residue was dissolved (H_2O). The (−) solution of **9** was made basic (NaOH) and extracted (Et_2O). The Et_2O was dried, filtered, and removed. The residue was

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(26) O. Exner, *Chem. Listy*, **47**, 869 (1953); *Chem. Abstr.*, **49**, 316 (1955).

dissolved (pyridine, 50 ml) and treated with 12.0 g (67.9 mmoles) of $C_6H_5SO_2Cl$. The solution was allowed to reflux for 1 hr. After cooling, H_2O was added to the mixture and the solid was harvested. The solid was dissolved (Et_2O) and the solution was washed (H_2O, dilute HCl). The Et_2O was dried, decolorized, filtered, and removed. The residue was crystallized (Et_2O) to give 16.0 g (73%) of **11**, mp 154–155°, $[\alpha]^{26}D$ −49 ± 1° (*c* 1.13, MeOH). *Anal.* ($C_{20}H_{23}NO_4S$) C, H, N.

(−)-*erythro*-2-Phenyl-2-[2-(1-benzenesulfonyl)piperidyl]ethanol (12).—To a cold suspension of 3.00 g of LAH in 500 ml of dry Et_2O and 200 ml of dry THF was added a solution of 12.0 g of **11** in 50 ml of THF. After 2 hr, the mixture was cooled and treated with 3 ml of H_2O followed by 3 ml of 15% NaOH solution and 9 ml of H_2O. The mixture was dried (Na_2SO_4) and stirred for 20 min. Following filtration the cake was washed (THF), the THF was removed, and the residue was crystallized (Et_2O) to give 10.1 g (91%) of **12**, mp 105–106°, $[\alpha]^{25}D$ −4.5 ± 0.5° (*c* 4.88, MeOH). *Anal.* ($C_{19}H_{23}NO_3S$) C, H, N.

(+)-*erythro*-2-Phenyl-2-[2-(1-benzenesulfonyl)piperidyl]ethyl Chloride (13).—A solution of 5.70 g of **12**, 3.53 g (20.0 mmoles) of tosyl chloride in 30 ml of pyridine and 50 ml of $CHCl_3$ was boiled for 24 hr. The cooled solution was acidified (HCl) and was extracted ($CHCl_3$). The $CHCl_3$ was dried, filtered, and removed. The residue was crystallized (C_6H_6). Recrystallization (MeOH) gave 4.00 g (66.7%) of **13**, mp 156–157°, $[\alpha]^{26}D$ +16 ± 0.5° (*c* 6.0, C_6H_6). *Anal.* ($C_{19}H_{22}ClNO_2S$) C, H, N.

(−)-1-Phenyl-1-[2-(1-benzenesulfonyl)piperidyl]ethylene (14).—To a solution of KNH_2 prepared from 469 mg of K dissolved in 150 ml of NH_3 was added 4.00 g of **15** in THF. When the red color faded, the NH_3 was allowed to evaporate. The residue was mixed with dilute HCl. The solution was extracted ($CHCl_3$). The $CHCl_3$ was dried, filtered, and removed. The residue was crystallized (Et_2O) to give 2.00 g (50%) of **15** which was recycled. Addition of petroleum ether to the mother liquor and partial removal of the Et_2O by boiling, afforded 500 mg (14%) of **14**, mp 87–88°, $[\alpha]^{23}D$ −66.8 ± 1° (*c* 1.80, C_6H_6). *Anal.* ($C_{19}H_{21}NO_2S$) C, H, N.

(−)-1-Benzenesulfonyl-2-benzoylpiperidine (15).—For 10 min, O_3 was passed through a solution of 500 mg of **14** in 50 ml of dry EtOAc at −75°. After 2 hr, excess O_3 was removed with N_2. After removing the EtOAc, 50 ml of pH 7 buffer containing 5 ml of H_2O_2 (30%) was added to the residue. In 1 hr, the crystals were harvested. Recrystallization (Et_2O–petroleum ether) gave 410 mg (81%) of **15**, mp 103–104°, $[\alpha]^{26}D$ −20 ± 1° (*c* 7.00, THF). *Anal.* ($C_{18}H_{19}NO_3S$) C, H, N.

(−)-α-[2-(1-Benzenesulfonyl)piperidyl]benzhydrol (16).—A solution of 329 mg of **15** in 20 ml of anhydrous Et_2O was added to a 30-ml solution of C_6H_5MgBr obtained by treating 146 mg of Mg with 942 mg of C_6H_5Br in Et_2O. After boiling the mixture for 3 hr, it was added to dilute HCl. The Et_2O was dried, filtered, and removed. The residue was crystallized (Et_2O) to give 200 mg (49%) of **16**, mp 167–169°, $[\alpha]^{20}D$ −67 ± 2° (*c* 1.19, THF). *Anal.* ($C_{24}H_{25}NO_3S$) C, H, N.

(*R*)-(+)-Piperidine-2-carboxylic Acid (17).—To 123 g of pyridine-2-carboxylic acid and 150 g of (+)-tartaric acid was added 1 l. of EtOH and 500 ml of H_2O. Dissolution was effected by gentle warming. Hydrogenation (2.0 g of PtO_2, 20°, 4.2 kg/cm²) resulted in gradual formation of a crystalline product during the 48–72 hr usually required to complete the reduction. The crystals were harvested and dissolved in a minimum amount of boiling H_2O. The mixture was filtered and diluted with 500 ml of EtOH. The crystals obtained on cooling were recrystallized to constant melting point, 191–192° dec, and specific rotation, $[\alpha]^{22}D$ +22.1 ± 1° (*c* 5.00, H_2O) [lit.[27] mp 192–193°, $[\alpha]^{20}D$ +22.3 ± 1° (*c* 6.4, H_2O)]. The enantiomeric salt, mp 191–192° dec (lit.[27] mp 191–193), $[\alpha]^{22}D$ −22.0 ± 1° (*c* 5.00, H_2O) [lit. $[\alpha]^{20}D$ −22.5 ± 1° (*c* 6.45, H_2O),[27] $[\alpha]^{25}D$ −20° (*c* 8.00, H_2O)[28]] was obtained by carrying out a $Pb(OAc)_2$ precipitation[27] of (+)-tartaric acid on the residue from the hydrogenation mother liquor and by subsequent resolution with (−)-tartaric acid. A 20-g sample of the (+)-bitartrate salt (mp 191–192°) afforded 8.85 g of **17** using Beyerman's[27] method: mp 276–277° dec, $[\alpha]^{21}D$ +25.5 ± 1° (*c* 3.00, H_2O) [lit.[27] mp 267° dec, $[\alpha]^{20}D$ +26.2 ± 1° (*c* 3.106, H_2O)]. *Anal.* ($C_6H_{10}NO_2$) C, H, N. The (−)-acid melted at 272–273° (lit.[28] mp 271–272°,[28] mp 266°[27]), $[\alpha]^{25}D$ −25.8 + 1° (*c* 3.10, H_2O) [lit. $[\alpha]^{20}D$ −25.4 ± 1° (*c* 2.85, H_2O),[27] $[\alpha]^{25}D$ −25.8° (*c* 5.00, H_2O)[28]].

Methyl (+)-1-Benzenesulfonylpiperidine-2-carboxylate (21).—To a solution of 5.0 g of **17** and 4.0 g of NaOH in 50 ml of H_2O was added 8.12 g of $C_6H_5SO_2Cl$. After 1 hr, the mixture was filtered. The aqueous was acidified (HCl) and extracted (Et_2O). The Et_2O was dried, filtered, and evaporated. The crude (+) residue (MeOH) was dissolved in dry MeOH. For 6 hr, HCl was passed through the solution at −75°. The MeOH and HCl were removed and the residue was crystallized (MeOH) to give 10.2 g (93%) of **21**, mp 61–63°, $[\alpha]^{29}D$ +54 ± 1° (*c* 3.03, C_6H_6). *Anal.* ($C_{13}H_{17}NO_4S$) C, H, N.

(−)-α-[3-(1-Benzenesulfonyl)piperidyl]benzhydrol (16) from 21.—A solution of 1.42 g of **21** in 25 ml of dry Et_2O was added to 50 ml of a solution of C_6H_5MgBr prepared by treating 729 mg of Mg with 4.71 g of C_6H_5Br in Et_2O. The mixture was boiled for 6 hr and was added to dilute HCl. The Et_2O was dried (Na_2SO_4), filtered, and removed. The residue was heated (50–60°) *in vacuo* to remove $(C_6H_5)_2$ and C_6H_5Br. The residue was crystallized (Et_2O–petroleum ether) to give 250 mg (12.3%) of **16**, mp 167–169°, $[\alpha]^{20}D$ −64 ± 2° (*c* 1.21, THF), mmp (of this alcohol with that prepared from **15**) 167–169°. *Anal.* ($C_{24}H_{25}NO_3S$) C, H, N.

(*R*)-(−)-α-(2-Piperidyl)benzhydrol Hydrochloride (19).—Dry HCl was passed for 12 hr through a suspension of 6.0 g (46.4 mmoles) of **17** in 50 ml of dry MeOH at 0°. The MeOH and HCl were removed. The residue was dissolved (H_2O). The solution was made basic (NaOH) and extracted ($CHCl_3$). The $CHCl_3$ was dried, filtered, and removed. The crude, (+) residue (Et_2O) was dissolved in 30 ml of dry Et_2O. The solution was added to 50 ml of a solution of C_6H_5MgBr prepared by treating 4.58 g of Mg with 31.4 g of C_6H_5Br in dry Et_2O. After 12 hr, the mixture was added to NH_4Cl solution. The solution was made basic (NaOH) and was mixed with Celite. The Celite cake obtained on filtration was washed with hot Et_2O. The Et_2O wash was used to extract the basic aqueous. The Et_2O was dried, filtered, and removed. The residue was crystallized (petroleum ether) to give 4.6 g (37%) of **19** free base, mp 98–99°, $[\alpha]^{26}D$ +58.2 ± 0.5° (*c* 4.00, MeOH) [lit.[8] mp 98–100° and 97–98°, $[\alpha]^{25}D$ +59.8° and +58.5° (*c* 2, MeOH)]. *Anal.* ($C_{18}H_{21}NO$) C, H, N. The HCl salt (**19**) prepared in Et_2O was recrystallized (MeOH–Et_2O): mp 295–296° dec, $[\alpha]^{26}D$ −41 ± 1° (*c* 5.00, MeOH) [lit.[8] mp 288–289° dec and 303–305° dec, $[\alpha]^{25}D$ −63.6° (*c* 1, H_2O) and $[\alpha]^{25}D$ −68.8° (*c* 2, H_2O)].

(−)-α-[2-(1-Benzenesulfonyl)piperidyl]benzhydrol (16) from 19.—To a refluxing solution of 300 mg of the (+)-base from **19** in pyridine was added 200 mg of $C_6H_5SO_2Cl$ in 3 ml of pyridine. Heating was continued for 30 min. The mixture was cooled and was added to dilute HCl. The acidic mixture was extracted ($CHCl_3$). The $CHCl_3$ was dried, filtered, and removed. The residue was crystallized (Et_2O–petroleum ether) to give 270 mg (59.2%) of **16**, mp 167–169°. Mixture melting points with the samples prepared from **15** and **21** were undepressed.

(*R*)-(−)-2-Benzhydrylpiperidine Hydrochloride (22).—To a solution of 600 mg of **19** in 30 ml of Et_2O was added 100 ml of NH_3, a few drops of dry EtOH, and 50 mg of Li chips. When the blue color disappeared, the NH_3 was evaporated. The residue was mixed with H_2O and the mixture was extracted (Et_2O). The Et_2O was dried, filtered, and removed. The oil was dissolved (Et_2O). The (+) solution was treated with HCl and the precipitate was crystallized (EtOH–Et_2O) to give 504 mg (73.7%) of **22**: mp 318–319°, $[\alpha]^{25}D$ −9 ± 1° (*c* 2.38, MeOH). *Anal.* ($C_{18}H_{22}NCl$) C, H, N.

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