The Stereochemistry of the Epimeric 2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanols[1]

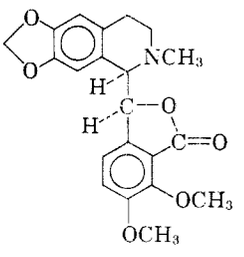
GLORIA G. LYLE AND MARC L. DURAND

Department of Chemistry, University of New Hampshire, Durham, New Hampshire 03824

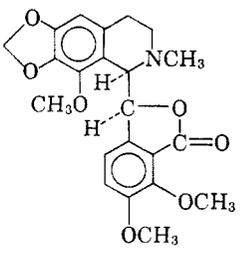
Received April 10, 1967

The synthesis of *erythro*- and *threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (**4** and **5**) has been accomplished by stereoselective processes and the relative stereochemistry of the two racemates has been established by a sequence of chemical conversions involving known mechanistic pathways. The comparison of the coupling constants of the benzylic protons of the nmr spectra with those of analogous α-aminocarbinols supported the assigned stereochemistry. These results showed that the amino alcohol **4** obtained by a catalytic reduction process was *erythro* while that prepared from a condensation reaction was *threo* (**5**). Resolution of the *threo* racemate gave the optically active enantiomers whose ORD curves on comparison with the known *threo*-2-amino-1,2-diphenylethanol (**10**) showed that the (−) isomer has the (1*S*:2*S*) configuration.

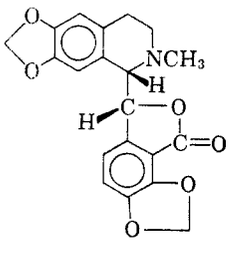
The total syntheses of a large number of alkaloids have been described, but no satisfactory stereospecific route to a phthalideisoquinoline derivative has been devised. The stereochemistry of two alkaloids of this family, hydrastine (**1**) and narcotine (**2**), has been determined[2] and both of the naturally occurring isomers of these alkaloids have been shown to have the *erythro* relationship of their asymmetric carbon atoms and the same absolute configuration.[2] This study was initiated in order to investigate new routes to partially reduced isoquinoline derivatives of known stereochemistry and the synthesis of bicuculline (**3**) was the ultimate aim. Although the stereochemistry of **3** has been deduced on the basis of nmr[3a] and optical rotation,[3b] unequivocal proof of either the relative or absolute configurations has not been obtained. A study of the ORD curves (see Experimental Section) in this laboratory of the phthalideisoquinolines suggested that bicuculline was enantiomeric in configuration to **1** and **2**, in agreement with previous conclusions.[4]



(−)-β-hydrastine (**1**)

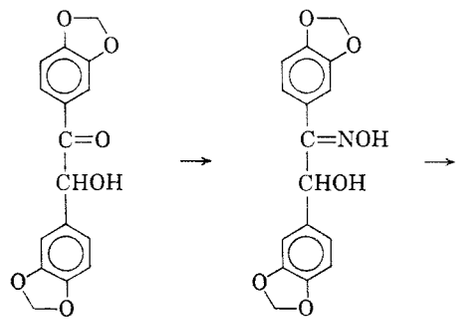


(−)-α-narcotine (**2**)

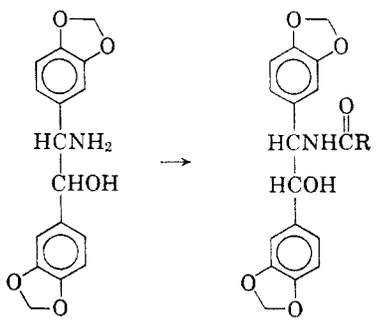


(+)-bicuculline (**3**)

The synthetic route required the facile preparation of optically active *erythro*- and *threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (**4** and **5**, respectively). Although syntheses of compounds of this structure had been carried out, proof of the relative stereochemistry of the resulting racemates was not available nor had the absolute configuration been determined. One synthesis involved the conversion of piperoin (**6**) to its oxime **7** followed by catalytic hydrogenation to the amino alcohol **4**.[5a] The oxime **7** had not been obtained pure by the previous workers, but it was crystallized in this work before reduction. The N-benzoyl (**8a**) and N-acetyl (**8b**) derivatives of **4** were readily obtained, but rearrangements to esters provided stereochemical information which will be discussed below. The fact that the synthesis was analogous to that used[5b] for the preparation of *erythro*-2-amino-1,2-diphenylethanol (**9**) suggested that **4** also had the *erythro* configuration.



6 **7**



4 **8a**, R = Bz; **b**, R = Ac

Attempts to convert **4** to the *threo* isomer **5** by the same route[5] used for rearranging **9** to its isomer **10**

(1) (a) Abstracted in part from the thesis submitted by M. L. D. to the Graduate School of the University of New Hampshire in partial fulfillment of the requirements for the Ph.D. degree. (b) This study was supported in part by Grant GM 07239 and continuation grants from the National Institutes of Health.

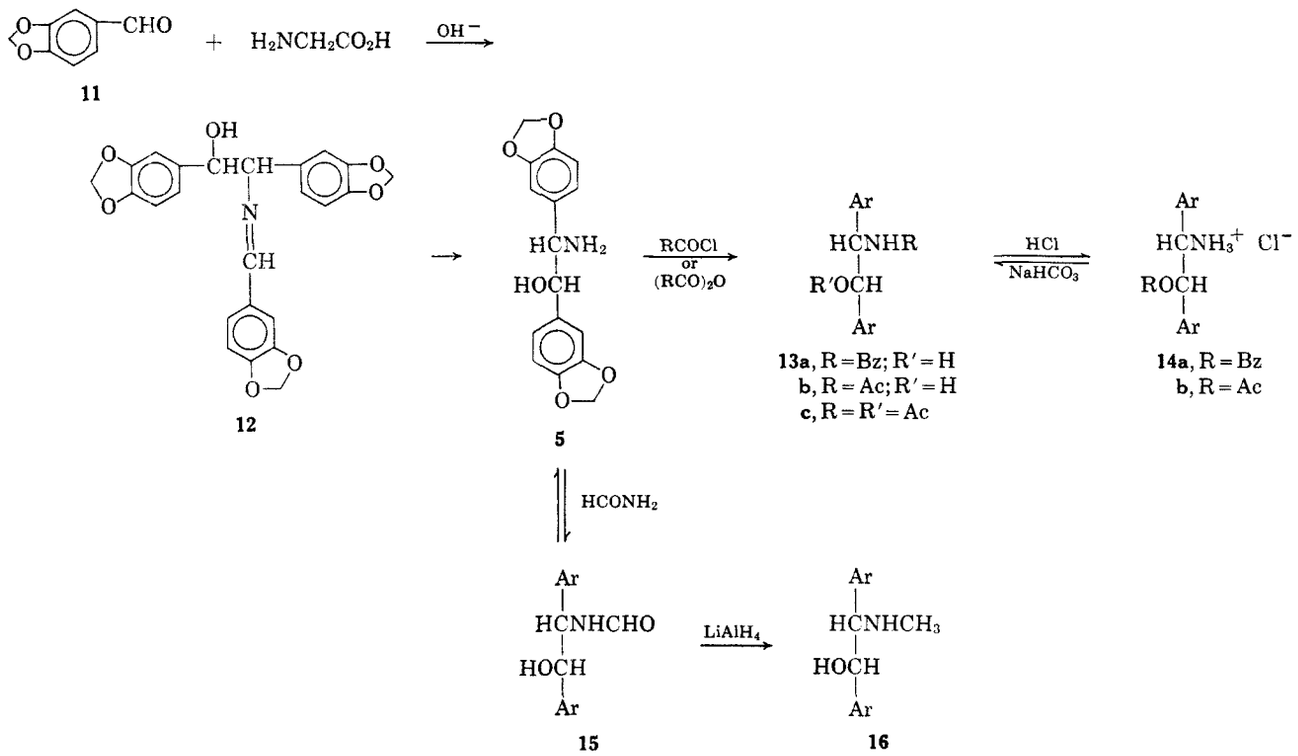
(2) M. Ohta, H. Tani, S. Morumi, and S. Kodira, *Chem. Pharm. Bull.* (Tokyo), **12**, 1072, 1080 (1964).

(3) (a) S. Safe and R. Y. Moir, *Can. J. Chem.*, **42**, 160 (1964); (b) K. Blaha, J. Hrbek, Jr., J. Kovar, L. Pijewska, and F. Santavy, *Collection Czech. Chem. Commun.*, **29**, 2328 (1964).

(4) The formulas are drawn as Fischer projections in the remainder of the paper. Most structures represent one enantiomer of the *dl* pair.

(5) (a) T. Kametani and K. Ohtsuki, *J. Pharm. Soc. Japan*, **74**, 621 (1954); (b) H. Weijland, K. Pfister, E. Swanezy, C. Robinson, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 1216 (1951).

SCHEME I



failed because of the difficulty of preparing the proper derivative (*vide infra*). A second amino alcohol isomeric with **4** was obtained by a modification of the condensation procedure of Read and Campbell.[6] Treatment of piperonal (**11**) with glycine in basic medium yielded the Schiff base **12** which was hydrolyzed to the amine hydrochloride with hydrochloric acid.

The free base **5** was obtained as a crystalline product which gave standard acyl derivatives **13** of the amino function. In acid, however, the acyl group migrated to the oxygen and the ester hydrochloride **14** was obtained. It was not possible to isolate the free base of the ester since the acyl group returned to the nitrogen atom on neutralization of the salt.

The amino alcohol **5** was converted to the N-benzoyl (**13a**), N-acetyl (**13b**), and O,N-diacetyl (**13c**) derivatives. The amide bands appeared in the infrared region at 1650–1640 cm^{-1} for all three compounds but **13c** also showed an ester carbonyl band at 1750 cm^{-1}. On treatment of **13a** or **13b** with acid, new products were isolated which appeared to be salts and for which the amide absorption bands had disappeared. The product **14a** obtained from the benzoyl derivative gave a carbonyl band at 1720 cm^{-1} and **14b** from the acetyl derivative showed carbonyl absorption at 1740 cm^{-1} indicative of ester groups. These reactions are consistent with the stereochemical conclusions described below.

Conversion of **5** to the formyl derivative **15** gave a product which had the usual carbonyl band at 1650 cm^{-1}. When **15** was treated with thionyl chloride followed by hydrolysis according to the procedure of Tishler and co-workers,[5b] the amino alcohol **5** was regenerated. Reduction of the formyl derivative **15** with lithium aluminum hydride yielded the N-methyl derivative **16** of the amino alcohol **5** (Scheme I).

Stereochemical Assignment

The study by Tishler, *et al.*,[5b] had shown that the *erythro*-2-amino-1,2-diphenylethanol (**9**) could be converted to the *threo* isomer **10** by formation of the N-formyl derivative followed by treatment with thionyl chloride. The authors assumed that the inversion of configuration at the oxygenated center occurred by formation of an intermediate oxazoline which was not isolated. They showed further that an analogous treatment of the formyl derivative of the *threo* racemate gave only starting material. The *erythro* isomer, therefore, could be converted to the *threo* product, but the sequence could not be reversed.

This reaction sequence was attempted with the amino alcohols **4** and **5** in view of the similarity of the problem. As cited above, **5** was readily converted to the formyl derivative **15** and back to itself, suggesting the *threo* configuration. Proof of this could not be obtained, however, since **4** did not yield a formyl derivative under a variety of conditions.

An alternative route was suggested by the facile migration of the benzoyl group of **13a**. The reaction appeared to be analogous to the N → O acyl migrations observed by Fodor and Kiss[7] in a variety of amino alcohols including derivatives of pseudotropine, the ephedrines (**17a,b**), and *cis*- and *trans*-2-aminocyclopentanol. In all of these compounds, a cyclic intermediate is assumed to form where the geometry permits

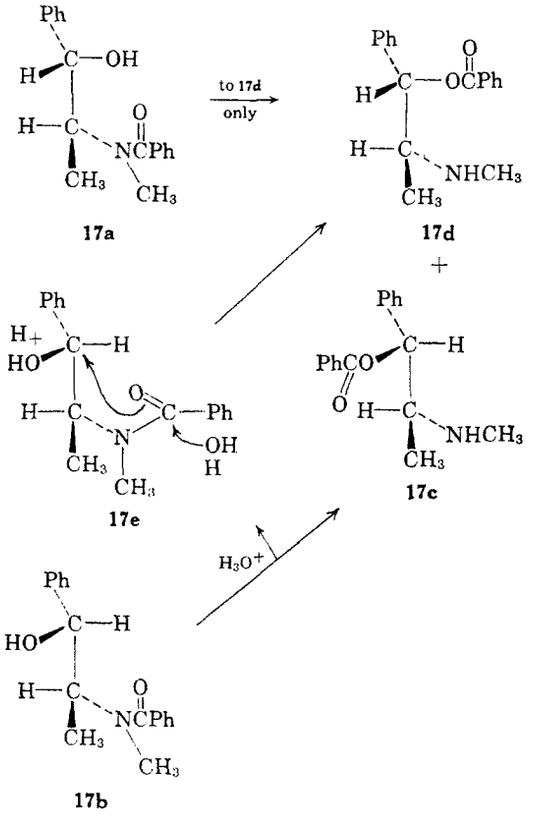
(6) J. Read and G. Campbell, *J. Chem. Soc.*, 2674 (1930).

(7) G. Fodor and J. Kiss, *J. Am. Chem. Soc.*, **72**, 3495 (1950); *J. Chem. Soc.*, 1589 (1952); *Nature*, **163**, 287 (1949).

migration of the benzoyl group, as in **17a**. In the case of the *erythro* isomer **17b**, the cyclic intermediate is unfavorable because the phenyl and methyl groups will be eclipsed and migration occurs only under vigorous conditions[8] with inversion at the hydroxyl-bearing carbon *via* an internal SN2 mechanism.

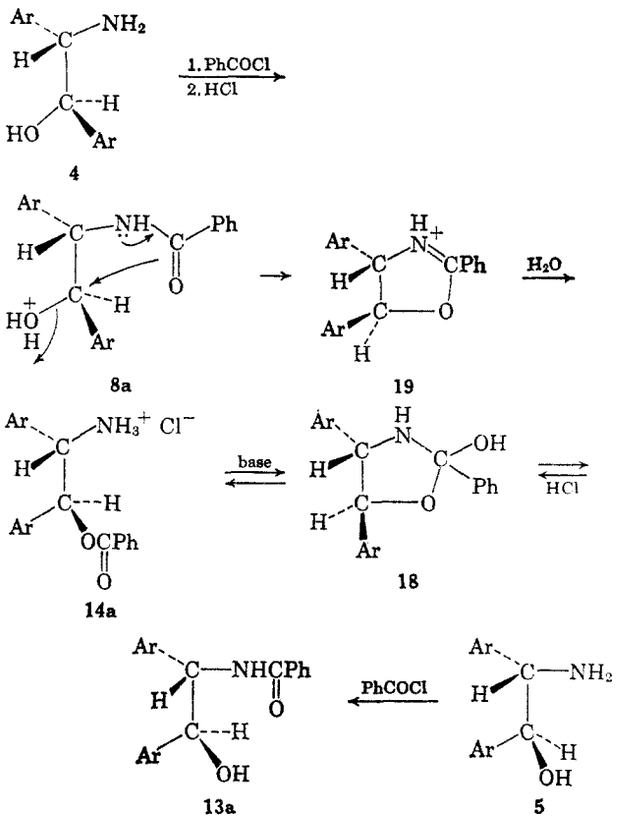
The migration of the benzoyl group in **17b** produced the same ester **17d** obtained from **17a** along with about 13% of the expected *erythro* ester **17c**. The author suggested[8] an intermediate such as **17e** and supported the participation of water by labeling experiments (Scheme II).

SCHEME II



In view of the possibility of similar migrations in the diaryl ethanolamines, the benzoyl derivatives **8a** and **13a** of **4** and **5**, respectively, were subjected to treatment at room temperature by dry hydrogen chloride in chloroform solution. From both reactions a product was isolated which had carbonyl absorption indicative of the benzoate ester hydrochloride **14a** and was, in fact, identical from the two reactions. On treatment with base, **14a** was converted to the amide **13a** prepared from the amino alcohol **5**. The analogy to the reactions described above[7,8] indicated that the amino alcohol **5** which gave the expected rearrangement with retention of configuration had the *threo* configuration. This reaction could proceed through the cyclic intermediate **18**. The *erythro* isomer **4** was converted to the benzamide **8a** which, however, on reaction with acid gave the same ester **14a** *via* a cyclic intermediate such as **19** formed with inversion of configuration of the hydroxyl center (Scheme III). The two aryl groups of the *erythro* isomer would be eclipsed if they formed an intermediate analogous to that (**18**) from the *threo* isomer and the reaction would seek an alternate pathway such as by **19**. The intermediacy of cyclic structures such as **18** and **19** is similar to the route postulated by Tishler and co-

SCHEME III



workers for the rearrangement of the N-formyl derivative **15** (Ar = Ph)[5b] and to that suggested by Welsh for the benzoyl derivatives of the ephedrines (**17**).[8] This pathway would be favored by the electron-releasing nature of the methylenedioxy groups of the aromatic rings, thus facilitating the removal of the water molecule by the backside attack of the oxygen of the benzoyl group. This is consistent with the ease of rearrangement in this system.

Analysis of the nmr spectra of the amino alcohols **4** and **5** in formic acid medium gave results supporting the above assignments of configuration. The coupling constants of the benzylic protons of **4** and **5** were 4.2 and 9.3 Hz, respectively. These compared with values of 4.2 and 9.4 Hz for *erythro* (**9**) and *threo* (**10**) isomers of 2-amino-1,2-diphenylethanol measured under the same conditions. Similar values have been found for the epimeric ephedrines.[9a] The virtual identity of the coupling constants of these compounds supported the assignment of configuration of *erythro* to **4** and *threo* to **5**.

The preparation of the optically active enantiomers of the *threo* racemate **5** was accomplished through the hydrogen tartrate salt.[6] The assignment of configuration was based on the shapes and amplitudes of the Cotton effect curves of the amine **5** and its salt as compared with the *threo* isomer of 2-amino-1,2-diphenylethanol (**10**).[9b] The ORD curves of the methylenedioxyphenyl compounds were of enhanced intensity

(8) L. H. Welsh, *J. Org. Chem.*, **32**, 119 (1967).

(9) (a) G. G. Lyle and L. K. Keefer, *ibid.*, **31**, 3921 (1966); (b) G. G. Lyle and W. Lacroix, *ibid.*, **28**, 900 (1963).

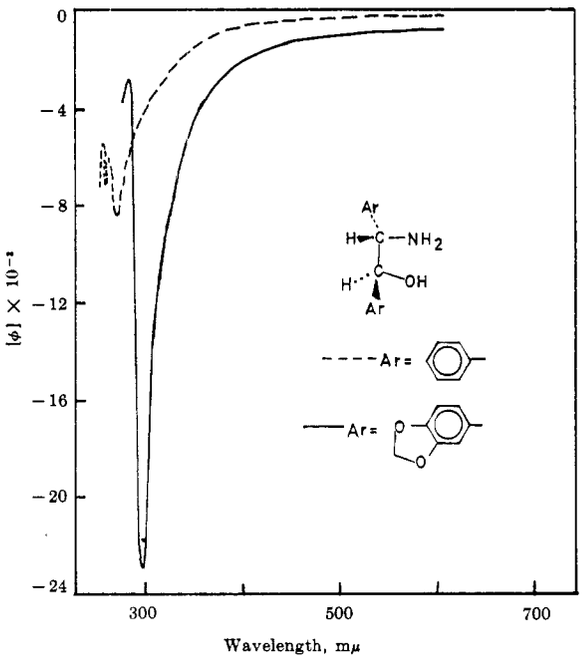


Figure 1.—Optical rotatory dispersion curves of *threo*-2-amino-1,2-diphenylethanol (- - - -) and *threo*-2-amino-1,2-bis-(3,4-methylenedioxyphenyl)ethanol (———).

compared with those of **10** (Figure 1), but the apparent negative Cotton effects of these compounds suggested the 1*S*:2*S* configuration for the levorotatory *threo* isomers. It is probable that the conformations are similar in these molecules which are so structurally similar. The curve for **5** gave a midpoint at longer wavelength (290 mμ) than in the case of **10** (275 mμ), but this bathochromic shift is consistent with the ultraviolet spectra of these compounds. The possibility exists that the complete Cotton effect is not yet achieved in the ORD curves (*e.g.*, these could be positive Cotton effects on negative backgrounds), but this question can best be answered by CD measurements. At present, the similarity of the curves is sufficient to predict identity of configuration.

Experimental Section[10]

Piperoin (6).—A solution of 210 ml of 95% ethanol, 167 ml of water, 159 g of piperonal (**11**), and 17 g of sodium cyanide was heated under reflux for 5 hr. After cooling overnight, the reaction product was separated by filtration and dried, giving 125 g (80%) of material, mp 95–113°, which after recrystallization melted at 114.5–118.5° (lit.[11] mp 119–120°).

Piperoin Oxime (7).—Piperoin (20 g), sodium acetate (12 g), and hydroxylamine hydrochloride (6 g) were mixed with 160 ml of water and 1200 ml of methanol. The reaction mixture was stirred at room temperature for 2 days, after which the methanol was evaporated, water was added, and the solution was extracted with ether. The ether extract was dried and evaporated, and the residue was recrystallized from benzene giving 7 g (34%) of product melting at 138.5–139°. The infrared spectrum showed a broad OH band at 3250 cm^{-1} and a shoulder at 1625 cm^{-1} indicative of the C=N stretching frequency.

Anal. Calcd for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16. Found: C, 61.41; H, 3.94.

(±)-*erythro*-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (4).—Piperoin oxime (0.85 g) was dissolved in 100 ml of absolute ethanol containing 0.3 g of Adams catalyst and 1 drop of concentrated hydrochloric acid. The mixture was submitted to 30 psig of hydrogen and allowed to shake for 36 hr. The solution was separated from the catalyst by filtration and evaporated giving a gummy substance which was dissolved in benzene. The benzene solution was dried and a small amount of hydrochloric acid in benzene was added, giving a solid mass of hydrochloride salt which was washed with ether and which melted over a wide range. The remaining hydrochoride salt was dissolved in water, made basic with ammonia, and extracted with ether. The extract was evaporated to dryness and the oil **4** formed a picrate which melted at 190–191° (lit.[5a] mp 190–191.5°). The nmr spectrum of the oily *erythro*-amino alcohol in formic acid gave two doublets for the two different benzylic type protons at τ 4.84 and 5.48 (J = 5.1 Hz). The N-benzoyl derivative **8a** was prepared from the reaction of **4** with benzoyl chloride, mp 201–203° (lit.[5a] mp 201–202°). The N-acetyl derivative **8b** was prepared from acetyl chloride and **4** and melted at 217–219° (lit.[5a] mp 218–220°).

N-Piperonylidene-(±)-*threo*-2-amino-1,2-bis-3,4-methylenedioxyphenyl)ethanol (12).—In this preparation, a modification of the procedure of Read and Campbell was employed.[6] Glycine (45 g) was dissolved in 400 ml of water containing 37 g of sodium hydroxide and this solution was added to 200 g of piperonal in 200 ml of methanol. The mixture was heated at reflux temperature for 15 hr and allowed to cool giving an orange solid. The residual alkaline mother liquor was decanted and the remaining solid was removed by filtration. The crude material was washed in the filter funnel with 50 ml of ethyl acetate; it was heated in a beaker of hot ethyl acetate (100 ml); and the insoluble substance was removed by filtration. In a typical reaction, an average yield of 65 g of product melting at 178–182° was obtained which, after further recrystallization from ethanol–ethyl acetate, melted at 181–182° (lit.[6] mp 177°).

(±)-*threo*-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (5).—The Schiff base **12** (25 g) was heated for 2 hr on the steam bath with 60 ml of 2 *N* hydrochloric acid. After cooling, the resulting solution was extracted several times with ether to remove piperonal. Excess ammonium hydroxide was slowly added to the stirring aqueous solution, giving a crude product which was removed by filtration. Treatment with Norit and recrystallization from hot ethyl acetate gave 13 g of a product (75%) melting at 161–162° (lit.[6] mp 159°). The nmr spectrum in formic acid showed the two doublets of the different benzylic protons at τ 4.92 and 5.48 (J = 9.2 Hz).

N-Benzoyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (13a).—The *threo*-amino alcohol **5** (1 g) in 40 ml of benzene was heated under reflux with 1.5 ml of benzoyl chloride for 30 min. The benzoic acid formed was removed by filtration and the filtrate was extracted with 15 ml of 2% sodium carbonate solution followed by extraction with the same volume of 2% hydrochloric acid and with water. The benzene solution was allowed to sit overnight and crystallization occurred giving 0.8 g of **13a** (60%) melting at 162.5–163.5°. The infrared spectrum of this compound was nearly identical with that of the benzoyl derivative **8b** of the *erythro* isomer (carbonyl band at 1640 cm^{-1}).

Anal. Calcd for $C_{23}H_{19}NO_6$: C, 68.14; H, 4.72. Found: C, 68.35; H, 4.76.

N-Acetyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (13b).—The free base **5** (1.0 g) was mixed with acetic anhydride (3 ml) and dissolved with the evolution of heat. On cooling, a substance immediately precipitated which was washed with 10 ml of ethyl acetate and 1.0 g of product (89%) was separated by filtration; it was recrystallized several times from hot ethyl acetate with a small amount of ethanol and melted at 209–210°. The infrared absorption spectrum indicated that an amide band (1650 cm^{-1}) was present.

Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99. Found: C, 62.88; H, 4.91.

O,N-Diacetyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (13c).—The amino alcohol **5** (1 g) was heated

(10) Infrared spectra were obtained on a Perkin-Elmer 337 spectrophotometer as mulls in halocarbon oil from 4000 to 1300 cm^{-1} and in Nujol from 1300 to 650 cm^{-1}. The nmr spectra were recorded on a Varian A-60 proton resonance spectrometer purchased with the assistance of Grant G-22718 to the University of New Hampshire from the National Science Foundation. Microanalyses were determined by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., and on an F & M Model 180 carbon, hydrogen, and nitrogen analyzer. ORD curves were measured on a Rudolph recording spectropolarimeter Model 260/655/850/810-609 using a 0.1-dcm tube and D-line rotations were measured in a 2-dcm tube on a Franz Schmidt and Haensch polarimeter.

(11) F. M. Perkin, *J. Chem. Soc.*, **54**, 164 (1891).

for 10 min on a steam bath with 10 ml of acetic anhydride and allowed to cool. The solution was poured into 100 ml of water and stirred for 24 hr. After cooling for 4 hr, a gummy solid separated from the milky mother liquor. This was separated by filtration and recrystallized from hot absolute alcohol giving 600 mg of cubic crystals (47%) melting at 176.5–177.5°; infrared carbonyl bands were found at 1650 (amide) and 1750 cm^{-1} (ester).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97. Found: C, 62.24; H, 4.97.

N-Benzylidene-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol.—A solution of the amino alcohol **5** (0.5 g) in hot absolute ethanol was added to 0.3 ml of benzaldehyde and the mixture was heated for 5 min. After cooling overnight, 0.45 g of large clear crystals were obtained (66%), which after recrystallization from absolute alcohol melted at 117.8–119°. A strong imine band at 1650 cm^{-1} was evident in the infrared spectrum.

Anal. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92. Found: C, 70.98; H, 5.02.

N-Formyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (15).—The hydrochloride salt of **5** (2.4 g) was mixed with formamide (7.5 ml) and heated at 150° for 20 min. After cooling, the solution was diluted with 75 ml of water and the solid product was separated by filtration and dissolved in hot methanol. Water was added and 1.3 g of a gummy substance (56%) was obtained which was dried in a desiccator. The dried material was recrystallized once from ethyl acetate to which Norite had been added. Upon further recrystallization from ethyl acetate a colorless, crystalline material was obtained which melted at 221–223° and which was identified as the formyl derivative **15** by the sharp NH band at 3400 cm^{-1}, a broad, bonded NH band at 3200 cm^{-1}, and a carbonyl amide band at 1650 cm^{-1}.

Anal. Calcd for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59. Found: C, 62.11; H, 4.44.

Treatment of the *threo*-N-Formyl Derivative 15 with Thionyl Chloride.—The N-formyl compound **15** (2.1 g) was added to 5 ml of thionyl chloride which had been cooled to 5° in an ice bath. After maintaining a temperature of 5° for 10 min, the reaction temperature was gradually raised to 22° (25 min) and the solution was poured over cracked ice giving a white solid. The mixture was heated under reflux for 2 hr, treated with Norit, and the product was separated by filtration. The colorless liquid was made alkaline with excess ammonium hydroxide and the resulting white solid was separated by filtration, washed with water, and dried. After two recrystallizations from ethanol, an amino alcohol **5** was obtained which melted at 161–162°; a mixture with the starting *threo*-amino alcohol **5** also melted at 161–162°.

N-Methyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (16).—The N-formyl derivative **15** (8.0 g), suspended in 100 ml of absolute ether, was added with stirring to 4 g of lithium aluminum hydride in 100 ml of absolute ether. The reaction was stirred for 3 hr and the lithium aluminum hydride was hydrolyzed with wet ether followed by addition of a 20% sodium hydroxide solution. The ether layer was separated from the salts by gravity filtration, dried over anhydrous potassium carbonate, and then evaporated. After two recrystallizations from ethanol, 3 g (39%) of **16** melting at 149.5–150.5° was obtained. The infrared spectrum showed no carbonyl band and the nmr spectrum gave the N-methyl singlet (3 H) at τ 7.78 and the two doublets of the benzylic protons at τ 5.51 and 6.60 (J = 9.0 Hz).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.42. Found: C, 64.48; H, 5.44.

The N-acetyl derivative prepared from **16** and acetic anhydride melted after recrystallization from ethyl acetate at 197–198°.

Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36. Found: C, 63.62; H, 5.41.

Reaction of the *erythro*-N-Benzoyl Derivative 8a with Hydrochloric Acid in Chloroform.—The *erythro*-amide **8a** (85 mg) was stirred for 5 hr at room temperature in 20 ml of chloroform which contained a large molar excess of hydrogen chloride gas, giving 80 mg of an ester hydrochloride (85%) which melted at 214–216°. The shift in the carbonyl absorption frequency in the infrared spectrum from 1650 to 1720 cm^{-1} indicated that a migration of the benzoyl group from nitrogen to oxygen had taken place. Recrystallization from absolute ethanol–ether gave a hydrochloride salt **14a** melting at 214–215°, which was the same melting point as that shown by the compound produced in analogous fashion from the *threo* isomer. A mixture melting point and a comparison of their infrared spectra confirmed their identity.

Anal. Calcd for $C_{23}H_{20}ClNO_6$: C, 62.50; H, 4.52. Found: C, 62.67; H, 4.74.

Treatment of the *threo*-N-Acetyl Derivative 13b with Hydrogen Chloride in Chloroform.—The N-acetyl derivative **13b** (2 g) was stirred for about 8 hr with an excess of hydrogen chloride in 90 ml of chloroform. The white substance obtained was desiccated and recrystallized from absolute ethanol with absolute ether to give 1.5 g of product (68%) melting at 172–173°. The material gave a positive Beilstein test and showed strong absorption in the infrared spectrum at 1740 cm^{-1} but showed no absorption at 1650 cm^{-1}, which supported the conclusion that the compound was O-acetyl-(±)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol hydrochloride (**14b**). Treatment of **14b** with sodium bicarbonate or with basic alumina gave back the amide **13b**.

Anal. Calcd for $C_{18}H_{18}ClNO_6$: C, 56.87; H, 4.74. Found: C, 56.53; H, 4.66.

Treatment of N-Benzoyl Derivative 13a with Hydrochloric Acid in Chloroform.—The amide **13a** (100 mg) was stirred for 5 hr at room temperature in 20 ml of $CHCl_3$ containing a large molar excess of anhydrous hydrogen chloride. The resulting amine hydrochloride **14a** (50 mg) melted at 214–215° and showed an infrared carbonyl absorption band at 1720 cm^{-1}, indicating that a migration of the benzoyl group from nitrogen to oxygen had taken place. Product **14a** was identical with the compound obtained on treatment of the *erythro* isomer **8a** with hydrogen chloride in analogous fashion.

Treatment of the O-Benzoyl Amine Hydrochloride 14a with Sodium Bicarbonate.—A few milligrams of the benzoate **14a** was suspended in ether and shaken in a separatory funnel with sodium bicarbonate solution. The suspension quickly dissolved in the ether layer and upon evaporation and drying a product was obtained which melted at 162.5–163.5°. A mixture melting point with the *threo*-benzamide **13a** previously prepared showed no depression.

Resolution of (±)-*threo*-2-Amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol (5).—The amino alcohol **5** was converted to the hydrogen tartrate salt with (+)-tartaric acid as previously described.[6] From 20 g of racemic **5**, 2.8 g of salt, mp 136–140°, $[\alpha]^{24}D$ +116° (*c* 0.84, water), and 4.0 g of salt, mp 203.5–205°, $[\alpha]^{24}D$ −104° (*c* 0.88, water), were obtained. The levorotatory salt was converted to the free amino alcohol with NH_4OH, yielding (−) **5**: mp 161.5–162.5°, $[\alpha]^{24}D$ −200.1° (*c* 0.48, 95% ethanol) (lit.[6] mp 164°, $[\alpha]D$ −196° (*c* 0.73, absolute ethanol)). The (+)-amino alcohol was similarly prepared: mp 162–163°, $[\alpha]^{24}D$ +192° (*c* 0.41, 95% ethanol) (lit.[6] mp 164°, $[\alpha]D$ +196° (*c* 0.46, absolute ethanol)). The ORD (Figure 1) in ethanol (*c* 0.10) was $[\phi]_{610}$ −1750°, $[\phi]_{589}$ −1870°, $[\phi]_{296}$ −23,200°, $[\phi]_{283}$ −1800°, $[\phi]_{280}$ −3610°.

The N-acetyl derivative of (+) **5** was prepared with acetic anhydride and on recrystallization from absolute ethanol melted at 228–229°, $[\alpha]^{24}D$ +32.7° (*c* 0.27, 95% ethanol). The rotation may be inaccurate owing to the tendency of the solution to form microcrystals.

Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.89. Found: C, 63.19; H, 5.04.

N → O Acyl Migration of N-Acetyl-(+)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol ((+) 13b).—The dextrorotatory *threo*-amide **13b** (1.9 g) was added to 80 ml of anhydrous chloroform containing a large molar excess of anhydrous hydrogen chloride. The solution was stirred at room temperature overnight and a white solid (1.68 g) was separated by filtration. Recrystallization from absolute ethanol and dry ether gave 1.2 g (57%) of product, mp 165–166°, $[\alpha]^{24}D$ +129° (*c* 0.79, 95% ethanol). The material gave a positive Beilstein test and showed strong absorption in the infrared region at 1740 cm^{-1} but no absorption at 1650 cm^{-1}, identical with the spectrum of racemic **14b**, confirming the assignment as (+) **14b**.

ORD Data of Alkaloids.—The curves were obtained in methanol solution using a 1-cm path length on a Rudolph recording spectropolarimeter. Previous literature[2] reported negative cotton effects for hydrastine and narcotine in 2 *N* HCl solution: narcotine (*c* 0.215, 0.00861), $[\phi]_{600}$ −518, $[\phi]_{589}$ −557, $[\phi]_{327}$ −20,200, $[\phi]_{297}$ +7680, $[\phi]_{290}$ 0, $[\phi]_{270}$ −21,100 (a = −278, midpoint 312 mμ; hydrastine (*c* 0.223, 0.00891), $[\phi]_{600}$ +103, $[\phi]_{589}$ +103, $[\phi]_{380}$ +1720 (br), $[\phi]_{350}$ 0, $[\phi]_{330}$ −2580, $[\phi]_{300}$ +9880, $[\phi]_{285}$ +8170, $[\phi]_{260}$ +18,900 (a = −125, midpoint 315 mμ); bicuculline

(*c* 0.208, 0.0114), $[\phi]_{600}$ +247, $[\phi]_{589}$ +247, $[\phi]_{339}$ +8400, $[\phi]_{304}$ −8400, $[\phi]_{280}$ −646, $[\phi]_{255}$ −7100, (*a* = +168, midpoint 324 mμ).

Registry No.—**4,** 13866-15-4; **5,** 13961-88-1; N-acetyl derivative of (+) **5,** 13866-26-7; **7,** 13866-17-6; **13a,** 13866-18-7; **13b,** 13866-19-8; **13c,** 13866-20-1; HCl salt **14a,** 13866-25-6; **15,** 13866-21-2; **16,** 13866-22-3; N-acetyl derivative of **16,** 13866-24-5; N-benzylidene-(+)-*threo*-2-amino-1,2-bis(3,4-methylenedioxyphenyl)ethanol, 13866-23-4.

Synthesis and Stereochemistry of Amino Alcohols and Derivatives in the 2-Amino-α-phenylcyclohexanemethanol Series

J. SZMUSZKOVICZ AND L. L. SKALETZKY

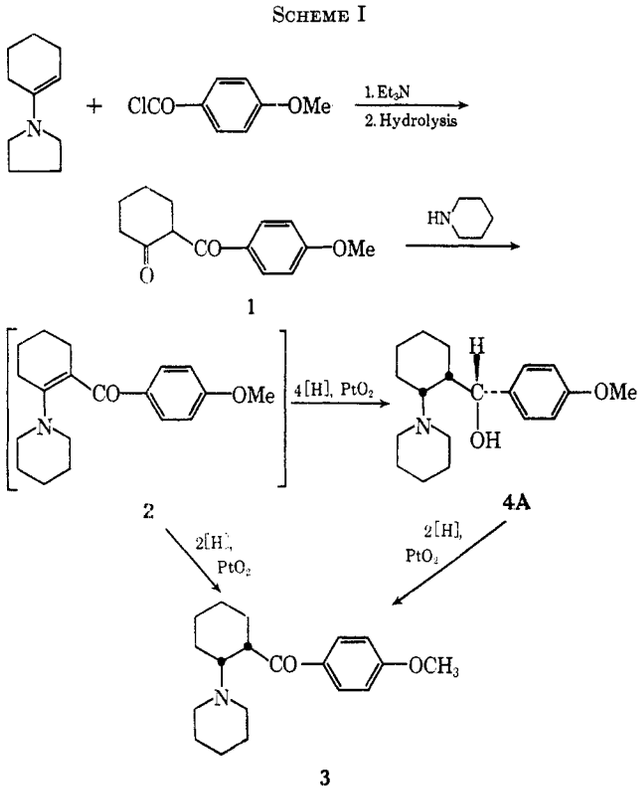
Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received April 10, 1967

Synthesis of the four amino alcohols, racemates **4A, 4B, 4C,** and **4D** of 2-(piperidino)-α-(*p*-methoxyphenyl)-cyclohexanemethanol, was accomplished as shown in Schemes I and II. The stereochemistry of these four racemates was determined by chemical transformations, nmr and infrared techniques, and the conformations assigned as α′, β, γ, and δ, respectively (Table I and Figure 1). Racemates **4A** and **4B** were also correlated with octahydrobenzoxazinones **8A** and **8B** (Scheme III and Table II). An interesting behavior of octahydrobenzoxazinone **8A** was noted: it isomerized to **8B** with trifluoroacetic acid without decarboxylation (Schemes III and IV). The relative stabilities of **4A, 4B, 4C,** and **4D** were further examined by synthesis of the corresponding methyl ethers **10A, 10B, 10C,** and **10D** and interconversions in this series (Scheme V). Conformations were assigned to these ethers (Figures 2 and 3). Several miscellaneous reactions of amino alcohols **4A** and **14** are described (Scheme VI).

Stimulated by the finding that amino alcohols such as piperidino alcohol **4** showed interesting diuretic activity, we embarked upon a synthetic and stereochemical investigation of this class of compounds.[1]

SCHEME I



The preparation of the required starting materials, 2-benzoylcycloalkanones, is illustrated in the case of 2-(*p*-methoxybenzoyl)cyclohexanone (**1**; see Scheme I above).

According to the general procedure for acylation of enamines,[2] treatment of 1-cyclohexen-1-ylpyrrolidine with *p*-methoxybenzoyl chloride afforded the desired compound **1.**

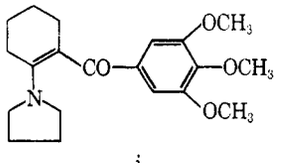
The next step, condensation of a 1,3-diketone with a secondary amine, is illustrated in the case of 2-(*p*-methoxybenzoyl)cyclohexanone (**1**) and piperidine (Scheme I), which gave the intermediate vinylogous amide (**2**). The ultraviolet spectrum of unpurified compound **2** in ether was compatible with the vinylogous amide structure and showed λ_{max} 264 mμ (*a* = 47.98) and 321 (7.41);[3] moreover, the nmr spectrum of the sample of **2** in carbon tetrachloride showed no absorption in the vinyl hydrogen region. Hydrogenation of **2** in ethanol in presence of platinum oxide gave the *cis*-alcohol **4A**[4] (see Scheme I and II), one of the two possible *cis* racemates. In some cases this type of amino alcohol could be prepared without isolation of the 1,3-diketone, but the yields were erratic.[5]

Preparation of the Four Amino Alcohol Racemates 4A, 4B, 4C, 4D and Assignment of *cis, trans* Configurations.—On treatment with trifluoroacetic acid (TFA), *cis*-alcohol **4A** was easily converted in 72%

(1) The pharmacological results of tests of a large number of compounds belonging to this class, only a few of which are described here, will be published elsewhere.

(2) See review of Enamines by J. Szmuszkovicz, *Advan. Org. Chem.*, **4,** 1 (1963).

(3) The ultraviolet spectrum (in ether) of the crystalline vinylogous amide (i) obtained from the condensation of 2-(3,4,5-trimethoxybenzoyl)-cyclohexanone with pyrrolidine showed λ_{max} 262 mμ (*a* = 33.26; ε 11,500) and 358 (*a* = 15.90; ε 5500).



i

(4) Capital letters after Arabic numerals designate specific diastereoisomers of the structure in question.

(5) *Cf.* R. D. Campbell and J. A. Jung, *J. Org. Chem.*, **30,** 3711 (1965), who have shown that the reaction of 1-cyclohexen-1-yl morpholine with various benzoyl chlorides gives rise to 2,2-diacylcyclohexanones.