TABLE VI

ELECTRONIC CHARACTER OF THE NITROGEN OF ANILINES AND BENZAMIDES RELATIVE TO THE *in Vitro* ACTIVITIES OF THE CORRESPONDING SULFONAMIDES

Substituent	Log $(1/C_r)^{a,b}$	σ_N	q_N	q_N^2
		Anilines		
4-NH_2	4.35	0.383	0.077	0.006
4-CH_3O	4.47	0.453	0.081	0.007
4-CH_3	4.57	0.453	0.081	0.007
H	4.80	0.477	0.083	0.007
4-Cl	4.80	0.459	0.082	0.007
4-NO_2	5.85	0.484	0.106	0.011
		Benzamides		
3-CH_3, 4-CH_3O	5.25	0.041	0.148	0.022
4-CH_3O	5.40[c]	0.035	0.148	0.022
3,4-CH_3	5.40	0.042	0.148	0.022
4-CH_3	5.40	0.036	0.148	0.022
3-CH_3	5.40	0.018	0.149	0.022
H	5.25	0.000	0.149	0.022
4-Cl	5.10[c]	0.027	0.148	0.022
4-CN	4.05[c]	0.000	0.151	0.023
4-NO_2	4.50[c]	0.000	0.153	0.023

[a] Minimum inhibitory concentration, C_r, against *E. coli*. [b] Data of J. K. Seydel, *Mol. Pharmacol.*, **2**, 259 (1966); J. K. Seydel and E. Wempe, *Arzneimittel-Forsch.*, **14**, 705 (1964). [c] We are extremely grateful to Dr. Seydel for testing these compounds for us.

TABLE VII

EFFECT OF HALIDE IONS ON AChE HYDROLYSIS OF ACh

Ion[a]	r, A[b]	$E^{\ddagger}$, ev[b]	Δ ev[b]	$E^{\ddagger}/\Delta$	μmoles of ACh split/hr per ml of enzyme[c]
F^-	1.36	−12.18	3.22	−2.33	9.1
I^-	2.16	−8.31	3.29	−2.52	35.6
Br^-	1.95	−9.22	3.64	−2.53	36.3
Cl^-	1.18	−9.94	3.92	−2.53	38.2

[a] Sodium salt in equivalent concentrations. [b] Data of ref 13. [c] B. N. Smallman and L. S. Wolfe, *Enzymologia*, **17**, 133 (1954).

with drug–receptor interactions and therefore show promise of greater utility in the study of drug action. The obvious extension of these equations to a form consistent with the Fujita–Hansch expression (eq 4) will be discussed in a forthcoming paper. It is readily shown that the Hansch parameter π may be considered a measure of drug–receptor interactions that fit the category of frontier-controlled reactions, but because of the demonstrated[10] importance of this quantity further development warrants separate consideration.

An interesting feature of the current approach results from the parallelism between the implications provided by eq 9 and 10[8,9] with regard to the principle of hard and soft acids and bases.[23,24] If future work bears out the presently promising indications, it may well turn out that a hard–hard, soft–soft complimentarity between the atoms of drug and receptor is a requisite for certain types of drug action.

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(23) R. G. Pearson, *J. Am. Chem. Soc.*, **85**, 3533 (1963).
(24) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

The Stereoisomers of α-(1-Aminoethyl)-*m*-hydroxybenzyl Alcohol

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A synthesis of the racemic and optically active isomers of *threo*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol is reported. A discussion of the absolute configuration of these compounds and α-methyl-*m*-tyramine is presented. Norepinephrine displacement from adrenergic neurons by the *threo* isomers is discussed.

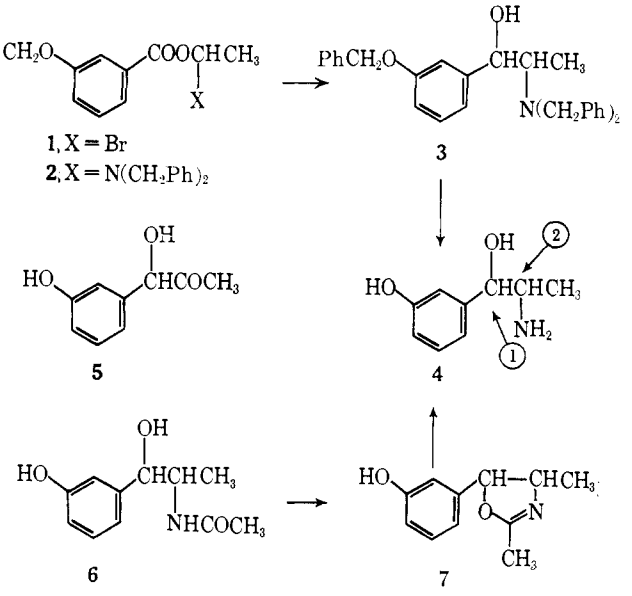
The sympathomimetic amine, metaraminol (**4**), (−)-*erythro*, has received extensive use as a pharmacological tool in studies on the mechanism of amine binding in adrenergic nerve endings.[1] Metaraminol is rapidly taken up by sympathetic tissue where it stoichiometrically displaces the normal neurotransmitter, norepinephrine.[2] Our interest in the relationship between amine stereochemistry and affinity for norepinephrine binding sites has led us to prepare the racemic and optically active forms of the *threo* isomer of **4**.

The method of Van Dijk and Moed[3] was used to prepare previously unreported racemic *threo*-**4** from *m*-benzyloxy-α-bromopropiophenone (**1**). Reduction of the amino ketone **2** with $LiAlH_4$ gave the *threo* alcohol **3** (Scheme I). Debenzylation of **3** to **4** was accomplished in two stages. Catalytic hydrogenation over a Pd–C catalyst in ethanolic HCl at room temperature removed two of the benzyl groups; the third was removed with a Pd–Al_2O_3 catalyst at higher temperature.

The optically active *threo* enantiomers **4** were prepared by reaction of the optically active *erythro* amides **6** with $SOCl_2$ followed by hydrolysis of the intermediate oxazolines with dilute HCl. This method has been used frequently in the past to convert *erythro* amido alcohols to *threo* amino alcohols in the ephedrine and norephedrine series.[4] Nmr spin-coupling constants for the hydrogens situated on C-1 and C-2[5] were 8.4 ± 0.2 Hz for the optically active and racemic products,

(1) P. A. Shore, *Pharmacol. Rev.*, **18**, 561 (1966).
(2) J. R. Crout, *Circulation Res.*, **18**, **19**, Suppl I, 120 (1966); J. R. Crout, H. S. Alpers, E. L. Tatum, and P. A. Shore, *Science*, **145**, 828 (1964).
(3) J. Van Dijk and H. D. Moed, *Rec. Trav. Chim.*, **78**, 22 (1959).
(4) H. K. Müller, *Ann.*, **599**, 61 (1956); H. Pfanz and H. Müller, *Arch. Pharm.*, **288**, 65 (1955).
(5) See formula **4** for numbering.

SCHEME I



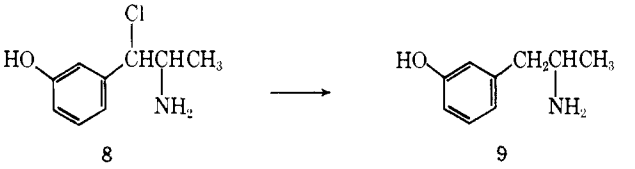
confirming that these compounds possess the predicted *threo* configuration.[6] No trace of the *erythro* product could be detected by nmr.

We have used the difference in nmr chemical shift of the benzyl hydrogens (H_1) in the *erythro* and *threo* isomers to study the isomerization of metaraminol in 6 *N* HCl. After several days at 100°, the *erythro* isomer was converted cleanly into a mixture of the two isomers containing 55 ± 5% of the *threo* isomer.[7] However on a preparative scale, the *threo* isomer could not be isolated in a pure state from the equilibration mixture.

The (−)-acyloin **5** has been shown by Tristram, *et al.*,[8] to have the *R* (rectus) configuration.[9] Since metaraminol has the *erythro* configuration and has been prepared from **5** by a method not involving inversion at the hydroxyl-bearing carbon atom,[10] the absolute configuration of metaraminol must be 1*R*,2*S*.[5,9,11] In addition, van Rossum[15] has quoted a personal communication from Dirkx that optical rotary dispersion studies have established the absolute configuration of metaraminol as 1*R*,2*S*.

Since synthesis of the optically active *threo*-**4** from the amides **6** proceeds with inversion of configuration at only the hydroxyl-bearing carbon atom, (−)-*threo*-**4** (prepared from 1*S*,2*R*-(+)-*erythro*-**6**) has 1*R*,2*R* absolute configuration. Similarly, (+)-*threo*-**4** has the 1*S*,2*S* stereochemistry.

In the course of this work, we also converted metaraminol to (+)-α-methyl-*m*-tyramine (**9**), establishing



the absolute configuration of this latter compound as *S* (sinister). This was accomplished by reaction of metaraminol with excess $SOCl_2$ to give the hydrochloride of **8** followed by catalytic reduction to **9**.

Biological Results.—Both of the optically active *threo*-**4** depleted mouse heart norepinephrine to approximately the same extent, having ED_{50}'s of about 30 mg/kg.[16] This is in sharp contrast to the *erythro* series in which metaraminol, ED_{50} of ~0.1 mg/kg, is much more active than its enantiomer.[17,18]

In the dog, the *threo* isomers exhibited sympathomimetic activity after intravenous administration. The 1*S*,2*S* isomer of **4** had marked pressor, inotropic, and chronotropic actions being about 0.1 times as active in this respect as metaraminol. The 1*R*,2*R* isomer was considerably less active than its enantiomer. It appears that norepinephrine depletion as measured in this work is a function of the combined stereochemistry at the amino- and hydroxyl-bearing carbon atoms and is not solely related to the stereochemistry at any one center.

Experimental Section[19]

***m*-Benzyloxypropiophenone**, bp 153–168° (0.1 mm),[20] was prepared in 95.5% yield from *m*-hydroxypropiophenone by the method of Suter and Ruddy.[21]

***m*-Benzyloxy-α-bromopropiophenone** (1).—A solution of 32.5 g (0.203 mole) of Br_2 in 50 ml of CH_2Cl_2 was added over 0.75 hr to a stirred solution of 50 g (0.208 mole) of *m*-benzyloxypropiophenone in 500 ml of CH_2Cl_2. N_2 was bubbled through the reaction during the addition and for an additional 3 hr after addition was complete. The CH_2Cl_2 solution was washed ($NaHCO_3$) and dried (Na_2SO_4). After filtering, solvent was removed under reduced pressure and the residue was dissolved in Et_2O, washed (5% NaOH, H_2O), dried (Na_2SO_4), and filtered. Removal of the ether solvent and recrystallization of the residue from hexane gave 50.5 g (78%) of the α-bromo ketone,[20] mp 46.5–49.0°. *Anal.* ($C_{16}H_{15}BrO_2$) C, H, Br.

***m*-Benzyloxy-α-dibenzylaminopropiophenone Hydrochloride (2).**—A solution of 33.5 g (0.105 mole) of *m*-benzyloxy-α-bromopropiophenone and 43.4 g (0.220 mole) of dibenzylamine in 400

(6) J_{H_1,H_2} = 4.2 Hz for the fumarate salt of metaraminol (*erythro*-**4**). Amino alcohols with the ephedrine (*erythro*) configuration have been reported to have J_{H_1,H_2} = 2.5–4.3 Hz while those having the pseudoephedrine (*threo*) configuration have J_{H_1,H_2} = 8–9.6 Hz; P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967); R. H. Uloth, J. Kirk, W. Gould, and A. A. Larsen, *ibid.*, **9**, 88 (1966); G. G. Lyle and L. K. Keefer, *J. Org. Chem.*, **31**, 3921 (1966); J. D. Hyne, *Can. J. Chem.*, **39**, 2563 (1961).

(7) These results are similar to those obtained by H. Emde [*Helv. Chim. Acta*, **12**, 377 (1929)] from rotation measurements for the isomerization of (−)-ephedrine with 25% HCl at 100°.

(8) E. W. Tristam, B. F. Powell, D. E. Williams, R. S. Tull, and J. M. Chemerda, presented at the Meeting in Miniature of the New York–New Jersey Section of the American Chemical Society, New York, N. Y., Jan 1962.

(9) Absolute configuration convention of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(10) M. Bockmühl, G. Ehrhart, and L. Stein, U. S. Patent 1,951,302 (1934); *Chem. Abstr.*, **28**, P3421 (1934).

(11) (−)-Ephedrine has been synthesized from (−)-1-hydroxy-1-phenyl-2-propanone by the same procedure.[12] The absolute configuration of this compound has been firmly established as 1*R*,2*S* by relation to D-(−)-mandelic acid and L-(+)-alanine,[13] substances which have been related to L-(+)- and L-(−)-glyceraldehyde.[14]

(12) K. Freudenberg, E. Schoeffel, and E. Braun, *J. Am. Chem. Soc.*, **54**, 234 (1932); G. Hildenbrandt and W. Klavehn, U. S. Patent 1,956,950 (1934); *Chem. Abstr.*, **28**, P4072 (1934).

(13) K. Freudenberg and F. Nikolai, *Ann.*, **510**, 223 (1934).

(14) J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1954).

(15) J. M. van Rossum, *J. Pharm. Pharmacol.*, **15**, 285 (1963).

(16) Determined 16–18 hr following intraperitoneal administration. Doses calculated as base weight, mg/kg.

(17) M. L. Torchiana, C. C. Porter, and C. A. Stone, *Arch. Intern. Pharmacodyn.*, in press.

(18) P. A. Shore, D. Busfield, and H. S. Alpers, *J. Pharmacol. Exptl. Therap.*, **146**, 194 (1964).

(19) All melting points, determined on a Uni-Melt Thomas–Hoover capillary melting point apparatus, are corrected; boiling points are uncorrected. Analytical results for all new compounds were within 0.4% of the calculated values. Ir and nmr spectra of all new compounds were consistent with the proposed structures. Reported spin-coupling constants were obtained in D_2O or DMSO with a Varian A60-A analytical nmr spectrometer. Optical rotations were determined with a Zeiss photoelectric precision polarimeter.

(20) E. Bumm, British Patent 711,905 (1954); *Chem. Abstr.*, **50**, 1914 (1956).

(21) C. M. Suter and A. W. Ruddy, *J. Am. Chem. Soc.*, **66**, 747 (1944).

ml of absolute EtOH was stirred at reflux for 6 hr. The cooled reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was extracted (Et_2O) which was then washed (H_2O) and dried (Na_2SO_4). After filtering and concentrating, the residue was dissolved in EtOAc, treated with ethanolic HCl, and cooled. A small amount of dibenzylamine hydrochloride was removed by filtration. Et_2O was added to the filtrate to precipitate 17.0 g (37.1%) of **2**, mp 142.9–145.9°. An analytical sample was obtained by further recrystallization from EtOAc–hexane. *Anal.* ($C_{30}H_{30}ClNO_2$) C, H, N.

***threo*-m-Benzyloxy-α-(1-dibenzylaminoethyl)benzyl Alcohol (3).**—The HCl salt **2** (4.26 g, 9.03 mmoles) was converted to the free base by shaking in a separatory funnel with 25 ml of H_2O, 5 ml of 10% NaOH, and 50 ml of Et_2O until all of the solid had dissolved. The ether extract was washed (H_2O) and dried ($MgSO_4$). The filtered Et_2O extract was added over 0.5 hr to a well-stirred mixture of 0.3 g of $LiAlH_4$ and 20 ml of dry Et_2O under N_2. After stirring for 4 hr at reflux, the reaction mixture was cooled in an ice bath and excess $LiAlH_4$ was decomposed with a saturated Na–K tartrate solution. The resulting viscous aqueous mixture was extracted several times (EtOAc). The combined extracts were washed (NaCl–H_2O), dried (Na_2SO_4), and filtered. Solvent was evaporated under reduced pressure to give 3.2 g (81.0%) of the *threo* alcohol, mp 117.6–122.1°, softened at 115°. Recrystallization from C_6H_6–hexane followed by recrystallization from MeOH gave 2.4 g (60.8%) of **3**, mp 122.6–124.6°. *Anal.* ($C_{30}H_{31}NO_2$) C, H, N.

Racemic *threo*-α-(1-Aminoethyl)-m-hydroxybenzyl Alcohol Fumarate (4).—A mixture of 1.0 g of a 5% Pd–C catalyst and 2.15 g (4.92 mmoles) of **3** in 50 ml of absolute EtOH containing 1.0 ml of 8 *N* ethanolic HCl was hydrogenated at 25° and atmospheric pressure. After 15 min, 2 equiv of H_2 were adsorbed. The catalyst was removed by filtration and replaced with 1.0 g of a 5% Pd–Al_2O_3 catalyst. One more equivalent of H_2 was taken up smoothly at 52° and atmospheric pressure. Catalyst was removed by filtration and the EtOH was evaporated under reduced pressure. The residue was dissolved in H_2O, neutralized ($NaHCO_3$), saturated with NaCl, and extracted several times (EtOAc). The EtOAc extracts were combined, dried (Na_2SO_4), filtered, and concentrated to 0.1 g of an oil. An additional 0.33 g of crude product was obtained by evaporating the aqueous extract to dryness under reduced pressure and extracting the residue (hot EtOAc). Treatment of the combined crude products with an equivalent amount of fumaric acid in EtOH and EtOAc gave the fumarate salt **4**, mp 212.4–214.4° dec, in 24.3% yield. Further recrystallization from MeOH–EtOAc gave an analytical sample, mp 215.4–216.4° dec. *Anal.* ($C_{22}H_{30}N_2O_8$) C, H, N.

(1*R*,2*S*)-α-(1-Aminoethyl)-m-hydroxybenzyl Alcohol (Metaraminol) Fumarate.—The fumarate salt of metaraminol, (−)-*erythro*-**4**, was prepared from the base by the same procedure used for the *threo* salt. Recrystallization from MeOH–EtOAc gave an analytical sample, mp 193.0–193.5° dec. *Anal.* ($C_{22}H_{30}N_2O_8$) C, H.

(1*R*,2*S*)-α-(1-Acetamidoethyl)-m-hydroxybenzyl Alcohol (6).—To a stirred solution of 75 g (0.237 mole) of (−)-*erythro*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (+)-hydrogen tartrate (metaraminol bitartrate) in 750 ml of H_2O was added 195 g of $NaHCO_3$. The solution was cooled to 5–10° and after adding 120 ml of Ac_2O dropwise over 30 min, the reaction mixture was allowed to warm to room temperature for 15–20 hr. Solid $NaHCO_3$ was added to neutralize any remaining acid. The crude product was isolated by extraction with three 400-ml portions of EtOAc which were then combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a syrup. This product was added to 200 ml of 10% NaOH and allowed to stand at room temperature for 24 hr. After cooling in an ice bath, concentrated HCl was added to adjust the pH to 1–2. The precipitated light tan solid was isolated by filtration and dried at 65° to a constant weight of 49 g of the hydrated amide, mp 95–102°, $[\alpha]^{25}D$ −18.5° (*c* 5, MeOH).

A hygroscopic analytical sample, mp 122.5–123.5°, was obtained after three recrystallizations from EtOAc–hexane. *Anal.* ($C_{11}H_{15}NO_3$) H; C: calcd, 63.14; found, 62.73.

(1*S*,2*R*)-α-(1-Acetamidoethyl)-m-hydroxybenzyl Alcohol (6) Hydrate.—The (+)-amide was prepared from (+)-*erythro*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol by the procedure used for the preparation of the (−)-amide. A sample was dried at 65° (0.2 mm) to give an analytical sample of the hydrate, mp 89–105°, $[\alpha]^{25}D$ +19° (*c* 2, MeOH). *Anal.* ($C_{11}H_{15}NO_3 \cdot H_2O$) C, H, N.

(1*R*,2*R*)-α-(1-Aminoethyl)-m-hydroxybenzyl Alcohol Fumarate (4).—A total of 5.0 g (0.0239 mole) of (1*S*,2*R*)-**6** was added in four portions over 0.5 hr to 40 ml of $SOCl_2$ in an ice bath. The reaction mixture was allowed to warm to 25° over 3 hr and then stirred at 40–45° for 15 min. After concentrating at 30–35° (15 min), C_6H_6 was added, and the mixture was reconcentrated. Fifty milliliters of 2 *N* HCl was added and the mixture was heated at reflux for 2 hr. The solution was concentrated under reduced pressure, 50 ml of *i*-PrOH was added, and the solution was reconcentrated. The residue was dissolved in 30 ml of H_2O, the pH was adjusted to 8.0 with K_2CO_3, and the product was extracted with four 30-ml portions of EtOAc. The extracts were combined, dried ($MgSO_4$), filtered, and concentrated. The residue, 0.95 g, was dissolved in EtOH and treated with 0.90 g of fumaric acid. The fumarate salt (0.63 g), mp 196.7–202.2° dec, was recrystallized from MeOH–EtOAc to give 0.27 g (5.0%) of (−)-*threo*-**4**, mp 208.2–209.7° dec, $[\alpha]^{25}D$ −28° (*c* 2, H_2O). *Anal.* ($C_{22}H_{30}N_2O_8$) C, H, N.

(1*S*,2*S*)-α-(1-Aminoethyl)-m-hydroxybenzyl alcohol fumarate (4) was prepared from (1*R*,2*S*)-**6** by the same procedure used for the (−)-*threo* isomer in 5.6% yield. The crude product was recrystallized from MeOH–EtOAc to give an analytical sample, mp 206.0–209.0° dec, $[\alpha]^{25}D$ +26° (*c* 2, H_2O). *Anal.* ($C_{22}H_{30}N_2O_8$) C, H, N.

Acid-Catalyzed Isomerization of (−)-*erythro*-α-(1-Aminoethyl)-m-hydroxybenzyl Alcohol (Metaraminol).—A solution of 300 mg of (−)-*erythro*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol in 1.5 ml of concentrated HCl and 1.5 ml of D_2O was heated with an oil bath at 100–105°. Aliquots were removed and analyzed by nmr for relative concentrations of the *erythro* and *threo* isomers using the *erythro*-H_1 doublet centered at approximately 4.9 ppm, J = 4.0 Hz, and the *threo*-H_1 doublet centered at approximately 4.5 ppm, J = 8.4 Hz. After 8 days at 100–105°, a near equilibrium mixture containing 55 ± 5% of the *threo* isomer was obtained. Further heating led to extensive decomposition.

(+)-*threo*-3-(2-Amino-1-chloropropyl)phenol Hydrochloride Hydrate (8).—Under N_2, 147.0 g of $SOCl_2$ was added slowly to a stirred solution of 31.8 g (0.190 mole) of (−)-*erythro*-α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol (metaraminol) in 120 ml of $CHCl_3$ at 25°. During the addition, the temperature was increased to 50° at which point a vigorous reaction ensued. Stirring and heating were discontinued until the foaming subsided. The reaction mixture was heated with stirring at 55° for 20 min. After cooling to room temperature, the tan precipitate was collected, washed with 400 ml of C_6H_6, and dried at 75° (1 hr) to yield 36.7 g (80.5%) of product, mp 118.0–121.0°, $[\alpha]^{25}D$ +71.2° (*c* 2, MeOH). *Anal.* ($C_9H_{15}Cl_2NO_2$) C, H, N, H_2O.

(*S*)-3-(2-Aminopropyl)phenol (9).—A solution of 35.7 g (0.148 mole) of (+)-*threo*-3-(2-amino-1-chloropropyl)phenol hydrochloride hydrate in 100 ml of absolute EtOH was hydrogenated (5% Pd–C catalyst) at 25° and atmospheric pressure until H_2 uptake ceased. After filtering, the reaction mixture was concentrated under reduced pressure. The residual oil was taken up in 50 ml of H_2O and treated with a solution of 100 g of K_2CO_3 in 100 ml of H_2O and the crude product was extracted with three 250-ml portions of BuOH. The BuOH extracts were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Recrystallization of the residue from EtOH–hexane gave 9.6 g of product, mp 155.0–158.0°. Sublimation at 100° (0.3 mm) yielded 9.5 g (42.4%) of **9**, mp 157.0–160.0°, $[\alpha]^{25}D$ +31.8° (*c* 2, MeOH). *Anal.* ($C_9H_{13}NO$) C, H, N.

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