Notes

The Optical Isomers of Metaraminol. Synthesis and Biological Activity

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(−)-Metaraminol[2] is a potent catecholamine depleter in heart tissue in a number of animal species.[3-6] Shore, Busfield, and Alpers[7] reported that (−)-metaraminol is rapidly taken up and retained by sympathetic nerve endings, generally with a stoichiometric exchange between metaraminol and norepinephrine. Crout[8] demonstrated a significant fall in blood pressure with (−)-metaraminol in four of six hypertensive patients. Besides an indirect action of norepinephrine release from tissue storage sites, (−)-metaraminol has been shown to have direct sympathominetic action on the effector organ.[9] A large variation in the relative direct and indirect vasopressor activity is seen among the four possible stereoisomers of ephedrine in the anesthetized dog with the (1*S*,2*R*) and (1*S*,2*S*) isomers exhibiting less direct activity than the (1*R*,2*S*) form.[10] Thus, it was of interest to prepare the four optical isomers of metaraminol to determine whether any of these retained the potent indirect release-depletion action seen with (−)-metaraminol (1*R*,2*S*) together with a reduction of the direct sympathomimetic property.

Since quantities of both (−)-metaraminol and the mother liquors from its resolution[11] were available to us, we chose to epimerize the benzylic hydroxyl rather than to synthesize and resolve the *threo* isomer. The route chosen (*i.e.*, introduction of a benzylic group prior to hydrolysis, while longer than direct hydrolysis of the oxazoline, permitted the final product to be readily isolated and purified (Scheme I).

Our results agree with those of Dirkx[12] who assigned the (1*R*,2*S*) configuration to (−)-metaraminol on the basis of optical rotory dispersion and lend further support to the utility of coupling constants of the benzylic hydrogen to demonstrate the *erythro* or *threo* configuration of phenethanolamines.[13] However, as anticipated, the Karplus equation fails to predict correct structures for the five-membered oxazoline ring. Both the *cis* (4*S*,5*R*) and *trans* (4*S*,5*S*) oxazolines were synthesized for comparison of their nmr data; the former had a coupling constant of 10 Hz and the latter a value of 7 Hz in $CDCl_3$.

Our biological results, summarized in Table I, indicate that only the (1*R*,2*S*) isomer of metaraminol shows appreciable activity in cathecholamine depletion and antihypertensive studies, although the acute toxicity of the various isomers does not vary appreciably. Similar results have been reported for ephedrine isomers.[9,10] The graded dose–response activity seen in this laboratory with subcutaneous (1*R*,2*S*)-metaraminol in the hypertensive rat agrees with the data of Brunner, *et al.*[14] The oral daily doses of (−)-metaraminol (1*R*,2*S*) that were found to be effective in the dog were similar to the effective dose range (6–22.5 mg) reported for (−)-metaraminol in man.[8] It would appear from the antihypertensive ineffectiveness of the other three isomers in the rat and dog, that a precise stereo configuration of metaraminol is critical for retention by the sympathetic nerve ending; an optical isomer of metaraminol possessing antihypertensive activity without potent direct vasopressor action was not found.

After our work was completed, Merck scientists published two papers on metaraminol. Saari, Raab, and Engelhardt[15] detailed the synthesis of the racemic and optically active *threo* isomers by a more direct but lower yield route than ours. Torchiana, Porter, and Stone[16] reported certain biological activities of the isomers. Our results supplement and corroborate those of the Merck group.

Experimental Section[17]

(1*S*,2*R*)-α-(1-Aminoethyl)-*m*-hydroxybenzyl Alcohol (−)-Bitartrate [(+)-*erythro*-Metaraminol (1)].—One liter of methanolic mother liquors from the preparation of (−)-metaraminol (+)bitartrate[18] was concentrated to give 224 g of amber syrup. This was dissolved in 400 ml of H_2O and neutralized with 55 g of NaOH in 50 ml of H_2O. Dilution with 600 ml of EtOH precipitated 110 g of disodium tartrate. After filtration the filtrate was concentrated and triturated with warm THF to cause the separation of another 26.7 g of disodium tartrate. Concentration of the THF solution yielded 90.1 g of syrup. A solution of 54.1 g of this syrup, 49.5 g of (−)-tartaric acid, 230 ml of MeOH and 65 ml of H_2O was allowed to stand at room temperature for 3.5 hr. Scratching the flask gave a crystalline precipitate which, when

(1) Deceased May 1968.

(2) α-(1-Aminoethyl)-*m*-hydroxybenzyl alcohol. The (−)-*erythro* isomer as the (+)-bitartrate is Pressonex® or Aramine®.

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(11) We are indebted to Mr. Raymond Wehnau of Winthrop Laboratories for a generous supply of the resolution liquors.

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(17) Melting points are not corrected for emergent stem errors. Nmr spectra were recorded on a Varian A-60 instrument using tetramethylsilane as an internal standard. We are indebted to some of our colleagues for technical assistance: to Dr. R. K. Kullnig and staff for nmr data, to M. K. Fleischer and staff for microanalytical data, and to Mrs. Gladys Barnett for rotational data.

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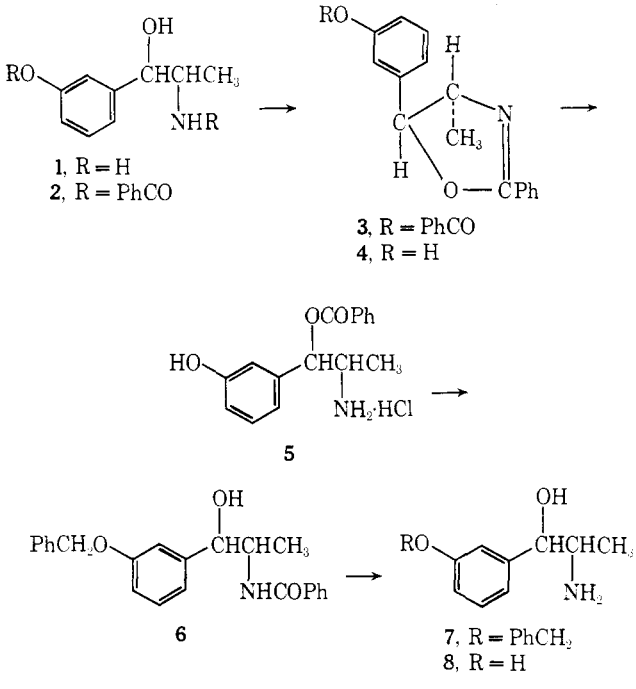
TABLE I
ANTIHYPERTENSIVE AND TISSUE CATECHOLAMINE DEPLETION ACTIVITY OF OPTICAL ISOMERS OF METARAMINOL

Optical isomer	Activity, mg of base/kg: Antihypertensive act. RH rat, AED_{30} sc	Hypertensive dog, MEAHD[a] oral	Tissue CA depletion rat heart, AED_{50} (hr)	Acute toxicity mouse, ALD_{50} iv
(1*R*,2*R*) or (−)-*threo*	>12	>24	8 (16)	92
(1*S*,2*S*) or (+)-*threo*	>12	>1.5	8 (16)	
(1*R*,2*S*) or (−)-*erythro*	1.1	0.07	0.06 (4)	90
(1*S*,2*R*) or (+)-*erythro*	>17	>2.1	>6 (4)	122

[a] Minimum effect antihypertensive dose is the daily minimum dose producing a sustained reduction in systolic/diastolic blood pressure in the unanesthetized dog.

SCHEME I



filtered and dried, weighed 52.8 g, mp 176–179°. Recrystallization from 9 vol of EtOH gave 91% recovery, mp 179–181°, $[\alpha]^{25}D$ +4.4° (*c* 1, H_2O). *Anal.* ($C_9H_{13}NO_2 \cdot C_4H_6O_3$) C, H, N.

N-[β-Hydroxy-α-methyl-*m*-(benzoyloxy)phenethyl]benzamide (2).—Benzoylation of either metaraminol base or its tartrate under Schotten–Baumann conditions gave a nearly quantitative crude yield of the dibenzoyl derivative. Recrystallization from EtOAc–hexane gave 78–83% yield of pure material: (1*R*,2*S*) or (−)-*erythro*, mp 145.5–147.5°, $[\alpha]^{20}D$ −66.6° (*c* 5, $CHCl_3$) [*Anal.* ($C_{23}H_{21}NO_4$) C, H, N]; (1*S*,2*R*) or (+)-*erythro*, mp 146–148°, $[\alpha]^{20}D$ +69.0° (*c* 5, $CHCl_3$) [*Anal.* C, H, N].

In some preparations tlc on Al_2O_3 plates developed with $CHCl_3$ showed the presence of a less polar impurity. Purification of a sample by dry column chromatography gave crystals melting at 173–175.5°. Nmr showed that this was the tribenzoyl derivative. Benzoylation in pyridine of the dibenzoyl derivative gave the same (1*R*,2*S*)-N-[(*m*,β-dihydroxy-α-methyl)phenethyl]benzamide dibenzoate, $[\alpha]^{25}D$ 19.2° (*c* 5, $CHCl_3$). *Anal.* C, H, N.

***trans*-5-(*m*-Benzoyloxy)phenyl-4-methyl-2-phenyl-2-oxazoline Hydrochloride (3).**—*erythro*-N-[β-Hydroxy-α-methyl-*m*-(benzoyloxy)phenethyl]benzamide (75 g) was dissolved in 400 ml of $CHCl_3$ and added at 0° to 200 ml of $SOCl_2$. After storing overnight at 5°, the reaction mixture was concentrated at 35° until a solid separated. Addition of Et_2O precipitated the product in 50–60% yields: (4*R*,5*R*) isomer, mp 154–156°, $[\alpha]^{25}D$ +30.1° (*c* 1, HOAc) [*Anal.* ($C_{23}H_{19}NO_3 \cdot HCl$) H, N; C: calcd, 70.13; found, 69.36]; (4*S*,5*S*) isomer, mp 153.5–156.5°, $[\alpha]^{25}D$ −64.9° (*c* 5, $CHCl_3$) (*Anal.* H, N; C: found, 69.54).

The mother liquor from the above preparation contains more product, but it is contaminated with **α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol dibenzoate hydrochloride.** This compound [(1*S*,2*S*) isomer] was prepared in 86% yield by refluxing 1 g of II·HCl, R = C_6H_5CO [(4*S*,5*S*)isomer] with 7.5 ml of H_2O and 2.5 ml of concentrated HCl for 30 min; mp 221–222°, $[\alpha]^{25}D$ −27.4° (*c* 0.5, 1:1 HOAc–H_2O). *Anal.* ($C_{23}H_{21}NO_4 \cdot HCl$) C, H, N.

***trans*-*m*-(4-Methyl-2-phenyl-2-oxazolin-5-yl)phenol (4).**—A mixture of 16 g of benzoyl oxazoline (**3**), 16 g of K_2CO_3, 60 ml of H_2O, and 48 ml of EtOH was stirred and refluxed for 7 hr. The EtOH was removed *in vacuo*, H_2O was added, and the product was collected by filtration: yield 91–95%, mp 172.5–175°. Samples were recrystallized from EtOAc for analysis: (4*S*,5*S*) isomer, mp 175–177°, $[\alpha]^{25}D$ 77.4° (*c* 1, EtOH), nmr showed C*H*O at 5.98 ppm with *J* = 8.6 Hz in TFAA and at 4.96 ppm with *J* = 7 Hz in $CDCl_3$ [*Anal.* ($C_{16}H_{16}NO_2$) C, H, N]: (4*R*,5*R*) isomer, mp 172–175°, $[\alpha]^{25}D$ −76.3° (*c* 1, EtOH) [*Anal.* C, H, N].

(4*S*,5*R*)- or *cis*-*m*-(4-Methyl-2-phenyl-2-oxazolin-5-yl)phenol.—A mixture of 2.68 g of (1*R*,2*S*)-metaraminol and 2.45 g of ethyl benzimidate was warmed under slight vacuum on a steam bath for 4 hr. The residue was converted to the hydrochloride, dissolved in 25 ml of boiling EtOH and filtered rapidly. Addition of 10 ml of Et_2O and cooling gave 2.90 g of crystals, mp 167.5–169.5°, $[\alpha]^{25}D$ −185.6° (*c* 1, EtOH), nmr on the crystalline base showed C*H*O at 6.55 ppm with *J* = 10 Hz in TFAA and at 5.55 ppm with *J* = 10 Hz in $CDCl_3$. *Anal.* ($C_{16}H_{15}NO_2 \cdot HCl$) C, H, N.

α-(1-Aminoethyl)-*m*-hydroxybenzyl Alcohol Benzoate Hydrochloride (5).—*trans*-(4-Methyl-2-phenyl-2-oxazolin-5-yl)phenol (30.4 g) was suspended in a solution of 30 ml of concentrated HCl and 240 ml of H_2O. The mixture was heated to boiling, filtered, and cooled to precipitate the product in 84–86% yield: (1*S*,2*S*) or (−)-*threo* isomer, mp 220–222°, $[\alpha]^{25}D$ −53.8° (*c* 1, MeOH), nmr showed C*H*O at 6.21 ppm with *J* = 8 Hz in TFAA [*Anal.* ($C_{16}H_{17}NO_3 \cdot HCl$) C, H, N]; (1*R*,2*R*) or (+)-*threo* isomer, mp 219–221°, $[\alpha]^{25}D$ +49.2° (*c* 1, MeOH) [*Anal.* C, H, N] (1*R*,2*S*) or (+)-*erythro* isomer, mp 244–245° dec, $[\alpha]^{25}D$ +83.5° (*c* 1, MeOH), nmr showed C*H*O at 6.25 ppm with *J* = 2 Hz in DMSO-d_6 [*Anal.* C, H, N].

N-[β-Hydroxy-α-methyl-*m*-(benzyloxy)phenethyl]benzamide (6).—A mixture of 5.80 g of α-(1-aminoethyl)-*m*-hydroxybenzyl alcohol benzoate hydrochloride, 20 ml of 2 *N* NaOH, 2.54 g of $C_6H_5CH_2Cl$, and 40 ml of DMSO was stirred overnight. H_2O (50 ml) was added and the mixture was cooled and scratched to induce crystallization. Recrystallization of the crude crystals from EtOAc–hexane gave 5.21 g of product (77%): (1*S*,2*S*) or (+)-*threo* isomer, mp 110–113°, $[\alpha]^{25}D$ +54.0° (*c* 1, $CHCl_3$) [*Anal.* ($C_{23}H_{23}NO_3$) C, H, N]; (1*R*,2*R*) or (−)-*threo* isomer, mp 107–110°, $[\alpha]^{25}D$ −54.2° (*c* 1, $CHCl_3$) [*Anal.* C, H, N].

α-(1-Aminoethyl)-*m*-(benzyloxy)benzyl Alcohol (7).—A mixture of 4.02 g of **6**, 10 g of NaOH, 10 ml of H_2O, and 20 ml of MeOH was stirred and refluxed for 6 hr. Addition of 50 ml of H_2O dissolved the gelatinous white precipitate. The product was extracted with Et_2O.

The (1*S*,2*S*) or (+)-*threo* isomer was isolated as the hydrochloride in 86% yield, mp 159–161°. *Anal.* ($C_{16}H_{19}NO_2 \cdot HCl$) Cl.

The (1*R*,2*R*) or (−)-*threo* isomer was isolated as the acetate in 73% yield, mp 170–172°, $[\alpha]^{25}D$ −24.7° (*c* 1, EtOH). *Anal.* ($C_{16}H_{19}NO_2 \cdot C_2H_4O_2$) C, H, N.

α-(1-Aminoethyl)-*m*-hydroxybenzyl Alcohol Acetate Salt (8).—α-(1-Aminoethyl)-*m*-(benzyloxy)benzyl alcohol acetate (10.8 g), 1.0 g of 10% Pd–C, 20 ml of HOAc, and EtOH to a total volume of 200 ml was hydrogenated at room temperature. Hydrogenation was complete in 10 min. Concentration of the filtered reaction mixture gave a syrup which was crystallized from 25 ml of EtOH to give 5.9 g (76%), mp 186–189°.

The (1*S*,2*S*) or (+)-*threo* metaraminol acetate had $[\alpha]^{25}D$ 34.6° (*c* 1, H_2O). *Anal.* ($C_9H_{13}NO_2 \cdot C_2H_4O_2$) C, H, N. The (1*R*,2*R*) or (−)-*threo* metaraminol acetate had $[\alpha]^{25}D$ −30.8° (*c* 1, H_2O): nmr showed C*H*O at 4.95 ppm with *J* = 8–9 Hz in D_2O. *Anal.* C, H, N.

Biological Methods.—Hypertension was induced in male Sprague–Dawley strain rats, weighing approximately 200 g, by the bilateral encapsulation method of Abrams and Sobin.[19] Antihypertensive activity of the test compounds following single subcutaneous medication was estimated in unanesthetized renal hypertensive rats in terms of AED_{50} values. The AED_{50} is defined as the approximate dose of the test compound, expressed in mg/kg, found to reduce the systolic blood pressure to a normotensive level in 50% of the animals tested. Systolic blood pressure was measured indirectly by means of the photoelectric tensometer method of Kersten, *et al.*,[20] utilizing three hypertensive rats per dose level. Systolic blood pressure of 130 mm or less was considered normotensive. Blood pressure was measured before and at 1, 2, 4, 6, 24, and 48 hr following medication.

Compounds were administered once daily in gelatin capsules for 5 consecutive days a week at each dosage level to unanesthetized hypertensive dogs. The methods for the induction of hypertension in dogs and the medication test procedure were described previously.[21]

Groups of four female Sprague–Dawley strain rats were used for the tissue catecholamine depletion studies. At least two groups were used for each medication level with duplicate assays on each group. Medications to 40 mg/kg were given subcutaneously 4–16 hr prior to sacrifice. After decapitation, hearts were immediately frozen over alcohol–Dry Ice. The frozen tissues were weighed and homogenized in 0.4 *N* $HClO_4$ and assayed by a modified alumina absorption procedure of Anton and Sayre.[22] Estimates were based on the ethylenediamine-stabilized trihydroxindole procedure of von Euler and Lishajko.[23] The AED_{50} was defined as the dose expressed as mg/kg of base producing a 50% reduction in tissue catecholamine content. AED_{50} values were estimated graphically.

Acute toxicity was expressed in terms of the approximate LD_{50}, ALD_{50}, by intravenous injection into male, Webster strain, albino mice weighing 22 ± 2 g. The compounds in aqueous solution were injected into groups of three mice at each of three or more dose levels.

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Amphetamine Analogs. II. Methylated Phenethylamines[1]

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In our previous work on amphetamine analogs,[2] 2,5-dimethoxy-4-methylamphetamine (DOM, **1**) was found to decrease the pentobarbital-induced sleeping time in mice. It exerted an effect nearly as pronounced as amphetamine.[2] Since the stimulating effect of methamphetamine is known to be more pronounced than its nonmethylated analog,[3] it would be interesting to find out if the introduction of a methyl group on the nitrogen of DOM (see **2**) would potentiate its effect both on the sleeping time and the disruption of animal behavior. The effect of mescaline (**3**) on the behavior of rats has also been reported.[4] Interest in what the activity would be when the aminopropyl side chain of **1** is replaced by an aminoethyl linkage led us to synthesize 2,5-dimethoxy-4-methylphenethylamine (**4**) as well as its N-methylated derivatives **5** and **6**.

Condensation of the 2,5-dimethoxy-*p*-tolualdehyde with nitromethane gave the β-nitrostyrene which was then reduced by $LiAlH_4$ to **4**. By a reductive formylation method, **4** was converted to its *N*,*N*-dimethyl analog **6**. The N-methyl compounds **2** and **5** were prepared by the methylation of Schiff's bases formed from benzaldehyde and the corresponding amine.

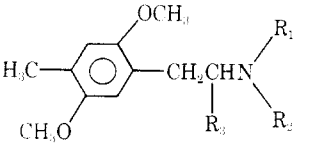
The results of the conditioned behavioral (VI) tests are expressed as ED_{50} (Table I). Compounds which were the most active in disrupting rat behavior were DOM (**1**) and **4**. Although **4** had three-fourths the activity of **1**, it is five times more potent than **3**. N-Methylation of both the phenylisopropylamine and the phenethylamine series resulted in compounds much less effective in behavioral disruption. A fivefold loss in activity was observed from **1** to **2**, and a 7.5-fold loss from **4** to **5**. However, no further decrease in activity was found when a second methyl group was introduced to **6**.

TABLE I
PHARMACOLOGICAL ACTIVITY OF METHYLATED PHENETHYLAMINES

No.	Mouse LD_{50} ± SE, mg/kg	Mouse sleeping time[a] Mean ± SE, min	p	Effect	Rat ED_{50},[b] μmole/kg
1	89 ± 4.2[c]	31.0 ± 1.9[c]	<0.001	↓	5.4
2	110 ± 3.0	40.5 ± 6.1	NS[d]	No	22
4	80 ± 1.3	98.0 ± 8.5	<0.001	↑	7.2
5	85 ± 4.1	46.4 ± 2.7	<0.10	↑	54
6	100 ± 1.6	39.5 ± 1.2	NS	No	46
3	315 ± 20.5[c]	34.4 ± 2.1[c]	<0.01	↓	38

[a] Sleeping time for control group is 41.0 ± 1.1 min. [b] Dose required for 50% decrease in conditioned response. [c] Data from ref 2. [d] p value larger than 0.10 was considered to be not significant (NS).

The effects of **1** and **3** in decreasing the pentobarbital sleeping time have previously been reported.[2] In this study, among the four compounds **2**, **4**, **5**, and **6**, both **4** and **5** were found to potentiate the sleeping time. It is interesting to compare the structures of **3** and **4** and to note that two opposite effects on the sleeping time resulted as the substituents on the benzene ring were varied. It remains to be determined if **3** and **4** have any effect on the metabolism of pentobarbital that could vary the sleeping time. As great as a fourfold difference in toxicity was also observed between **3** and **4** (Table I).



1, $R_1 = H$; $R_2 = H$; $R_3 = CH_3$
2, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_3$
4, $R_1 = R_2 = R_3 = H$
5, $R_1 = R_3 = H$; $R_2 = CH_3$
6, $R_1 = R_2 = CH_3$; $R_3 = H$

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