Anal.—Calc. for $C_{25}H_{19}F_6NO_2$: C, 62.63; H, 3.99; N, 2.92. Found: C, 62.66; H, 4.20; N, 3.24.

L-*6-(5-Amino-5-carboxypentyl)-6,7-dihydro-2,10-bis(trifluoromethyl)-5H-dibenz*[c,e]*azepine Dihydrobromide* (*IIIe*)—α-Carbobenzoxy-L-lysine (1.29 g, 0.004 mole), 1.52 g (0.004 mole) of V, and sodium hydrosulfite (5.3 g, 0.03 mole) were allowed to react by the procedure of Hawthorne *et al.* (6). The reaction mixture was filtered to give a white solid, which was recrystallized from acetone to give 0.5 g (19%), mp 199–201°. This solid was treated with 5 ml of hydrobromic acid–acetic acid (30–32%) at room temperature for 1 hr. Upon addition of ether, the product precipitated and was collected. Recrystallization from ethanol–ether gave 0.43 g (93%) of white powder, mp 230–232°; NMR: δ 7.4–8.0 (m), 5.0–5.5 (m), 3.4–4.2 (m), 2.8–3.2 (m), and 1.0–2.1 (m) ppm.

Anal.—Calc. for $C_{22}H_{22}F_6N_2O_2 \cdot 2HBr$: C, 42.47; H, 3.89; N, 4.50. Found: C, 43.07; H, 4.28; N, 4.53.

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Synthesis and Activity of (*R*)-(−)-*m*-Trimethylacetoxy-α-[(methylamino)methyl]benzyl Alcohol Hydrochloride: A Prodrug Form of (*R*)-(−)-Phenylephrine

SUN-SHINE YUAN and NICOLAE BODOR ˣ

Abstract □ Optically pure (*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride was synthesized by the following sequence: (*R*)-(−)-phenylephrine was condensed with acetone in the presence of calcium carbide to give an oxazolidine derivative and then treated with thallous ethoxide in ether followed by trimethylacetyl chloride to yield the phenolic ester. Finally, the oxazolidine ring was cleaved by one equivalent of hydrogen chloride in ethanol. Condensation of phenylephrine with benzaldehyde, with or without solvents, gave either 1,1,2-trimethyl-4,6-dihydroxy-1,2,3,4-tetrahydroisoquinoline or a mixture of side-chain oxazolidine and the tetrahydroisoquinoline. Condensation of epinephrine with opianic acid in pyridine also gave a tetrahydroisoquinoline only. When applied on rabbit eyes, the prodrug (*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride exhibited an unexpected, three times higher mydriatic activity than the corresponding racemic prodrug and was 15 times more active than the parent, (*R*)-(−)-phenylephrine.

Keyphrases □ Phenylephrine prodrug—(*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride synthesized, mydriatic activity screened □ Prodrugs—(*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride synthesized, mydriatic activity screened □ Mydriatic agents, potential — (*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride synthesized and screened

Phenylephrine, *m*-hydroxy-α-[(methylamino)-methyl]benzyl alcohol, is a well-known sympathomimetic amine and is used topically as a nasal decongestant and as a mydriatic. Its levorotatory isomer is generally used because, as in the case of other adrenergic agents, the (*R*)-(−)-form is significantly (about 10 times) more potent (1) than the dextro-form. Therefore, the racemic mixture is about one-half as active as the (*R*)-(−)-form. High therapeutic concentrations (up to 10%) even of the (*R*)-(−)-form must, however, be used topically because of the low permeability of the molecule due to its polar, hydrophilic functions. Consequently, only small portions of the relatively high concentration solutions used are absorbed topically (for example, transcorneally).

To overcome this disadvantage, the use of more lipophilic prodrugs[1] (2) was suggested (3). Indeed, one corresponding racemic ester, *m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol, was shown to possess higher biological activity and greater stability than the parent drug, (*R*)-(−)-phenylephrine, as a result of the greater lipid solubility and the masking of the labile phenolic hydroxyl group. As shown later, the increase in biological activity is significant; the racemic prodrug is about five times more effective as a mydriatic than the (*R*)-(−)-phenylephrine [the same mydriatic effect could be achieved with a 0.5% solution of (±)-prophenylephrine as with a 2.5% solution of (−)-phenylephrine solution]. As in the case of the parent drug,

[1] The expression "prodrug" denotes a derivative of a known and proven drug, which, due to its improved physicochemical properties, increases the bioavailability of the proven drug. The derivative is transformed by an enzymatic or chemical process into the proven drug before reaching it and/or at the site(s) of action. As applied in the present context, an improved form of phenylephrine is a prodrug form which, due to its improved topical (*i.e.*, corneal) absorptivity, increases the topical bioavailability of the drug. After absorption, the drug is released by an enzymatic and/or chemical process. See, for example, Ref. 2.

a further increase in the relative potency can be expected by using the corresponding pivalate derivative of the levorotatory isomer, which should be about 10 times more potent than the parent (−)-phenylephrine.

Since there is no direct way for selective acylation of the phenolic hydroxyl group in phenylephrine, the (±)-pivalylphenylephrine was prepared (3) by reduction of the acylated *N*-benzylketone precursor. Resolving the racemic pivalate would be an unreliable way for obtaining the (*R*)-(−)-form, since it would be difficult to prevent the cleavage of the ester function during the resolution, particularly during the epimerization step in recycling.

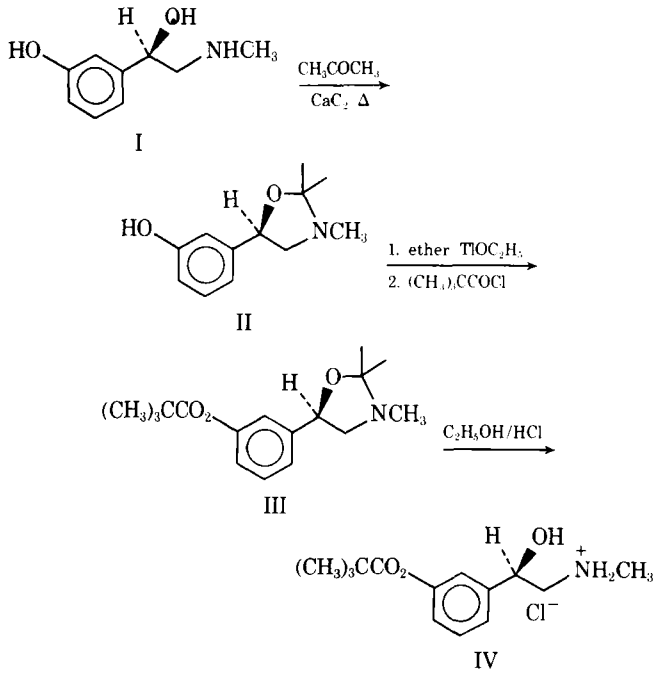
This paper reports an easy synthetic procedure for preparing the optically pure (*R*)-(−)-enantiomer of *m*-pivalylphenylephrine as well as its comparative mydriatic effectiveness.

DISCUSSION

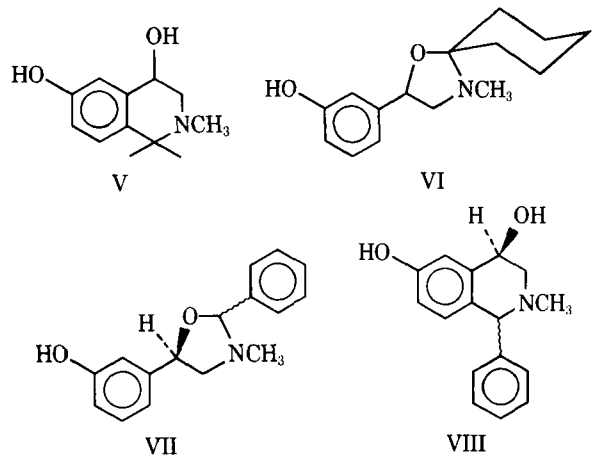
Chemistry—The synthetic scheme started from the optically active (*R*)-(−)-phenylephrine (I, Scheme I), in which the ethanolamine side chain was protected by the formation of an oxazolidine ring (4) as the result of the reaction with a ketone such as acetone. Compound II was easily formed using calcium carbide (5) as a dehydrating agent. The oxazolidine (II) was treated with thallous ethoxide in ether (6), and the formed thallous salt was reacted without isolation with trimethylacetyl chloride to afford the ester (III). The oxazolidine ring was then cleaved using one equivalent of hydrogen chloride in ethanol to give the optically active prodrug (IV). The optical purity of IV was confirmed by hydrolyzing it back to the parent, (*R*)-(−)-phenylephrine hydrochloride, and no change in the original optical rotation was observed.

Scheme I obviously can be used for the synthesis of the racemic derivative and for the preparation of other esters by replacing the pivalyl chloride with the corresponding acyl halide.

Contrary to these results, Kametani *et al.* (7) showed that the condensation of phenylephrine and acetone in alcoholic solvents did not result in the oxazolidine (II) but the tetrahydroisoquinoline isomer (V). On the other hand, Bretschneider (8) observed that the condensation of phenylephrine with cyclohexane, used also as the solvent, at higher temperature resulted in the oxazolidine (VI) in good yield.

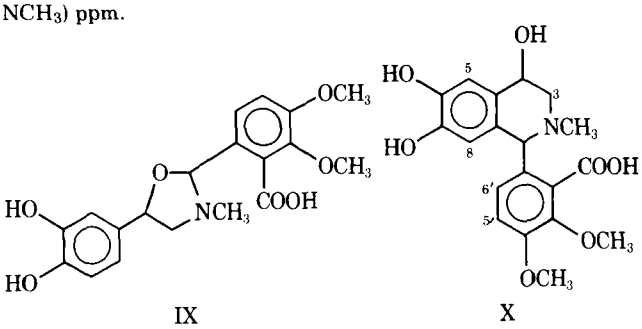


Scheme I



The preparation of the oxazolidine (VII) was recently reported (9) from benzaldehyde and phenylephrine. However, when using the experimental conditions given, the present authors found that a 1:1 mixture of VII and the tetrahydroisoquinoline (VIII) was formed. The condensation products were always formed exclusively in neat benzaldehyde or in pyridine as a solvent.

The analogous condensation of epinephrine with opianic acid in pyridine, as reported by Bretschneider (8), was reexamined. It was found that the product was not the oxazolidine (IX), as suggested by Bretschneider (8), but the tetrahydroisoquinoline (X), as clearly supported by the NMR spectrum (1 *M* Na_2CO_3 in D_2O): δ 7.1 (s, 2, C-5′ and C-6′), 6.8 (s, 1, C-5), 6.1 (s, 1, C-6), 5.2 (m, 1, C*H*OH), 4.4 (s, 1, CHN), 3.9 (s, 6, OCH_3), 3.2–2.6 (*ABX*, 2, CH_2N), and 2.2 (s, 3, NCH_3) ppm.



Mydriatic Activity—The mydriatic effectiveness of the pivalate (IV) thus prepared was then studied to confirm the expected increased activity as compared to (*R*)-(−)-phenylephrine and to the (*R,S*)-(±)-pivalate. The mydriatic activity was studied by measuring the change in pupillary diameters of male and female white rabbit eyes as a function of time and dose, following instillation of 50 μl of isotonic solutions of the compounds studied. Figure 1 shows the comparison

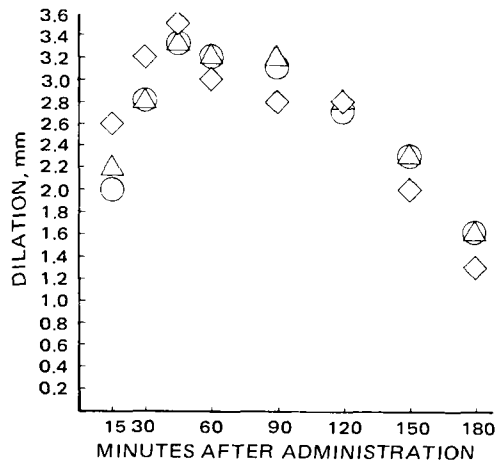


Figure 1—*Equivalent mydriatic responses of rabbit eyes elicited by (−)- and (±)-m-pivalylphenylephrine hydrochloride (prodrug) and (−)-phenylephrine hydrochloride solutions. Key: ○, 0.15% (−)-prodrug; △, 0.5% (±)-prodrug; and ◇, 2.5% (−)-phenylephrine.*

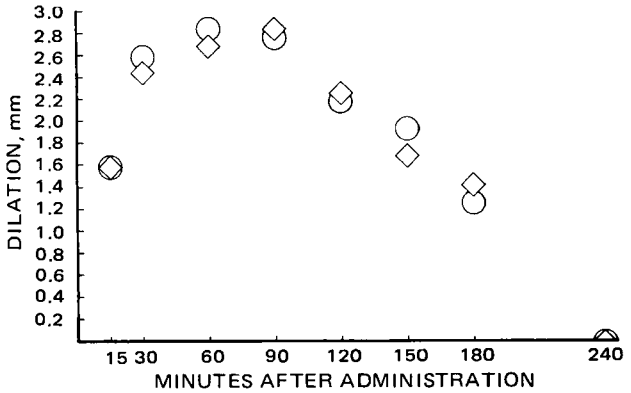


Figure 2—*Equivalent mydriatic responses of rabbit eyes elicited by (−)- and (±)-m-pivalylphenylephrine hydrochloride (prodrug) solutions. Key: ◇, 0.1% (−)-prodrug; and ○, 0.3% (±)-prodrug.*

of 2.5% of (*R*)-(−)-phenylephrine hydrochloride[2], 0.5% of (*R,S*)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride, and 0.15% of (*R*)-(−)-*m*-trimethylacetoxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride.

All compounds tested elicited practically the same mydriatic effect at the concentrations studied, which proves the significant increase in activity by pivalation of the *m*-hydroxyl group of phenylephrine. However, it is surprising that the (*R*)-form was approximately three times more active than the racemic (*R,S*)-pivalate. To verify this unexpected result, numerous studies were performed using other concentrations (Fig. 2). The data verify that the (*R*)-(−)-form is indeed three times more active than the racemic form and, thus, about 15 times more potent a mydriatic as the free (*R*)-(−)-phenylephrine. The free (*R*)-(−)-phenylephrine is faster acting, although the effect decreases faster.

EXPERIMENTAL[3]

(*R*)-(−)-2,2,3-Trimethyl-5-(*m*-hydroxyphenyl)-1,3-oxazolidine (II)—(*R*)-(−)-Phenylephrine (I) (9.0 g, 0.05 mole), acetone (1 liter), and calcium carbide (4.0 g, 0.06 mole) were heated together at reflux with stirring for 24 hr. The solid material formed was filtered off, and the filtrate was concentrated *in vacuo*. The residue was crystallized in an acetone–hexane mixture to give 7.0 g of II (70%), mp 118–120°, $[\alpha]_D^{25}$ −17.9° (c 5, CH_3OH); IR (KBr): 2980, 2860, 2700, 1600, 1450, 1260, and 1120 cm^{-1}; NMR (CD_3COCD_3): δ 7.4–6.6 (m, 4), 5.2 (broad, 1), 5.0 (t, 1, J = 7 Hz), 3.3 (dd, 1, J = 7 and 9 Hz), 2.7 (dd, 1, J = 7 and 9 Hz), 2.4 (s, 3), and 1.3 (s, 6) ppm.

Anal.—Calc. for $C_{12}H_{17}NO_2$: C, 69.6; H, 8.2; N, 6.8. Found: C, 70.0; H, 8.4; N, 6.7.

A solution of II in methanol was stored at room temperature for 12 hr. After evaporating the solvent, pure (*R*)-(−)-phenylephrine was isolated.

(*R*) - (−) - 2,2,3-Trimethyl-5-(*m*-trimethylacetoxyphenyl)-1,3-oxazolidine (III)—To a solution of II (1.32 g, 6.38 mmoles) in 60 ml of ether was added thallous ethoxide (1.59 g, 6.38 mmoles), and the mixture was stirred at room temperature for 1 hr. Pivalyl chloride (0.79 ml, 6.38 mmoles) was then added, and stirring was maintained for 2 additional hr. The solid material formed in the reaction was filtered, and the filtrate was evaporated to dryness to give 1.8 g of an oily product, III (95%); $[\alpha]_D^{25}$ −10.6° (c 5, C_2H_5OH); IR (neat): 2960, 1760, 1610, 1590, 1480, 1450, 1370, 1360, 1260, 1230, 1140, and 1105 cm^{-1}; NMR (CCl_4): δ 7.4–6.8 (m, 4), 5.0 (t, 1, J = 7 Hz), 3.3 (dd, 1, J = 7 and 9 Hz), 2.8 (dd, 1, J = 7 and 9 Hz), 2.3 (s, 3), 1.4 (s, 9), and 1.3 (s, 6) ppm.

Anal.—Calc. for $C_{17}H_{25}NO_3$: C, 70.2; H, 8.6; N, 4.8. Found: C, 70.1; H, 8.8; N, 4.9.

(*R*)-(−)-*m*-(Trimethylacetoxy)-α-[(methylamino)methyl]benzyl Alcohol Hydrochloride (IV)—Compound III (1.8 g, 6.2 mmoles) in 60 ml of ether was treated with hydrogen chloride gas until the solution was no longer turbid. This mixture was then evaporated to dryness, and the residue was dissolved in a small amount of ethanol and then diluted with hexane. The hydrolysis and crystallization took place in the solution to give 1.2 g of the final product, IV (70%), mp 128–130°; $[\alpha]_D^{25}$ −36.7° (c 5, C_2H_5OH); IR (KBr): 3370, 2960, 2795, 2420, 1750, 1610, 1590, 1460, 1240, and 1110 cm^{-1}; NMR (CD_3COCD_3–D_2O): δ 7.5–6.8 (m, 4), 5.3 (dd, 1, J = 5 and 10 Hz), 3.8 (broad, 3), 3.4 (m, 2), 2.9 (s, 3), and 1.4 (s, 9) ppm.

Anal.—Calc. for $C_{14}H_{22}ClNO_3$: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.4; H, 7.7; N, 4.6.

A solution of IV (1 g) in 10 ml of methanol containing 1 ml of concentrated hydrochloric acid was heated to reflux for 24 hr. The solvent was then removed *in vacuo* to give 0.7 g (90% yield) of (*R*)-(−)-phenylephrine hydrochloride, $[\alpha]_D^{25}$ −47.0° (c 5, C_2H_5OH) [lit. (10) $[\alpha]_D^{25}$ −46.2° (c 1)].

Condensation of Phenylephrine and Benzaldehyde—Racemic phenylephrine (0.83 g, 5 mmoles), benzaldehyde (0.55 ml, 5 mmoles), and benzene (100 ml) were placed in a flask attached with a Dean–Stark trap. The mixture was heated to reflux for 8 hr until 0.1 ml of water was collected. The solvent was partially removed, and the oxazolidine (VII) crystallized first (0.5 g, 38%), mp 215° dec.; IR (KBr): 3200, 1600, 1480, 1290, 1050, and 1000 cm^{-1}; NMR (CD_3COCD_3): δ 10.9 (m, 1), 7.4–6.5 (m, 9), 4.8 (m, 1, C-5), 4.6 (s, 1, C-2), 3.2–2.5 (m, 2, CH_2N), and 2.3 (s, 3, NCH_3) ppm.

The mother liquor was then evaporated to give 0.5 g (38%) of VIII, mp 110–112° [lit. (7) mp 90°]; IR (KBr): 3600, 3240, 2400, 1620, 1510, 1460, 1330, 1310, and 1240 cm^{-1}; NMR (CD_3COCD_3): δ 7.4–7.0 (m, 7), 6.4 (s, 1), 5 (m, 1), 4.2 (s, 1), 3.2 (m, 1, OH), 3.2 (m, 1), 2.5 (m, 1) and 2.2 (s, 3, NCH_3) ppm.

Condensation of Epinephrine with Opianic Acid—Racemic epinephrine (183 mg, 1 mmole) and opianic acid (210 mg, 1 mmole) were heated along with pyridine (10 ml) at 80–90° for 2 hr. After cooling, the product crystallized to give 150 mg of IX (40%), mp 245° dec. [lit. (8) mp 230° dec.); IR (KBr): 3500, 2460, 1610, 1580, 1530, 1480, 1450, 1420, 1380, 1280, 1260, and 1060 cm^{-1}. As in Bretschneider's study (8), purification attempts did not yield analytically pure material.

Mydriatic Experiments—Solutions of IV, the (*R,S*)-isomer of IV (3), and (*R*)-(−)-phenylephrine hydrochloride were prepared by dissolving the material in 0.9% saline solution. Standard doses of 50 μl were applied to male and female rabbit eyes, and pupillary changes were measured in a light- and temperature-controlled room. Amounts of dilation, in millimeters, were measured at 15-min intervals in the 1st hr and at 30-min intervals thereafter. The differences in the same animal between the pupil diameter of the eye with drug applied against the other eye with saline were observed. Each point is the average of five and/or six independent experiments.

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[x] To whom inquiries should be directed.

[2] Neo-Synephrine.

[3] Melting points were taken in a Thomas Hoover capillary melting-point apparatus and are uncorrected. NMR spectra were measured in a Varian T-60 NMR spectrometer. IR spectra were taken in a Beckman 33 instrument. Optical rotations were measured using a Carl Zeiss polarimeter. Elemental analyses were performed by the medicinal chemistry laboratory of the University of Kansas, Lawrence, Kans.