Synthesis and Antimalarial Activity of Dibenz[c,e]azepine Derivatives

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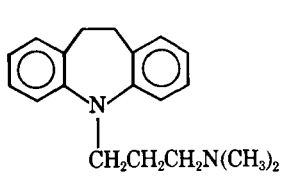
Abstract □ A series of 6-alkyl-2,10-bis(trifluoromethyl)-5*H*-dibenz[*c,e*]azepines were synthesized *via* a condensation reaction between 5,5′-bis(trifluoromethyl)-2,2′-diformylbiphenyl and the appropriate amine. These compounds were screened for antimalarial activity and were found to be inactive.

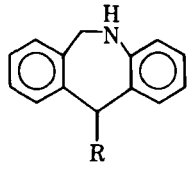
Keyphrases □ Dibenz[*c,e*]azepine derivatives—synthesis, antimalarial activity □ Antimalarial agents, potential—dibenz[*c,e*]azepines synthesized and screened □ Structure–activity relationships—dibenz[*c,e*]azepines synthesized and screened for antimalarial activity

A number of aminoalkyl derivatives of 10,11-dihydrodibenz[*b,f*]azepine (1) related to imipramine (I) were prepared and evaluated for their psychotropic activity (2). Other dibenz[*b,e*]azepine derivatives (II) were prepared due to the relationship of such compounds to the antihistamines of the benzylaniline type (3). The dibenz[*c,e*]azepines (III) were investigated primarily for their α-adrenergic blocking activity; one example, azepetine (III*a*), is a potent α-adrenergic blocking agent and has been used to treat peripheral vascular diseases (4).

After completing a study of the antimalarial activity of a series of 9,10-dihydrophenanthrene amino alcohols (5) with 3- and/or 6-trifluoromethyl substituents (IV), it was decided that an investigation of the antimalarial activity of the analogous 6-alkyl-2,10-bis(trifluoromethyl)-5*H*-dibenz[*c,e*]azepine derivatives (III*b*–III*e*) would be of interest.



I



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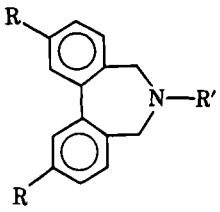
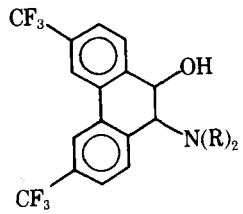
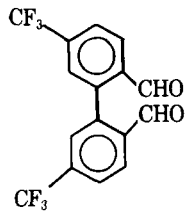


III*a*: R = H, R′ = $CH_2CH{=}CH_2$
III*b*: R = CF_3, R′ = $(CH_2)_3N(CH_2CH_3)_2$
III*c*: R = CF_3, R′ = $CH_2CH{=}CH_2$
III*d*: R = CF_3, R′ = $CH(COOH)CH_2C_6H_5$
III*e*: R = CF_3, R′ = $(CH_2)_4CH(NH_2)COOH$



IV



V

EXPERIMENTAL[1]

Biological Activity—The dibenz[*c,e*]azepine derivatives (III*b*–III*e*) were tested for antimalarial activity using mice infected with *Plasmodium berghei*[2] or chicks infected with *P. gallinaceum*. None of the compounds tested caused any increase in mean survival time of more than 2 days in the mouse screen, and they were considered inactive in the chick screen. The compounds tested were not lethal to mice at the dosages tested (640 mg/kg).

Chemistry—Compounds III*b*–III*e* were prepared by allowing 5,5′-bis(trifluoromethyl)-2,2′-diformylbiphenyl (V) to react with an appropriate amine in the presence of sodium hydrosulfite by the procedure of Hawthorne *et al.* (6). The dialdehyde V was prepared by the ozonolysis of 3,6-bis(trifluoromethyl)phenanthrene by the procedure described (5).

*6-(3-Diethylaminopropyl)-6,7-dihydro-2,10-bis(trifluoromethyl)-5*H*-dibenz*[c,e]*azepine Dihydrochloride* (*III*b)—According to the procedure of Hawthorne *et al.* (6), V (1.7 g, 0.005 mole) was allowed to react with *N,N*-diethylaminopropylamine (1.3 g, 0.01 mole) and sodium hydrosulfite (6.0 g, 0.038 mole). The reaction mixture was extracted with chloroform (3 × 25 ml), and the chloroform solution was dried (sodium sulfate) and treated with 50 ml of saturated chloroform–hydrochloric acid. The resulting solution was taken to dryness *in vacuo*, yielding 2.3 g (88%) of hygroscopic crystalline material, mp 108°; NMR: δ 7.2–7.8 (m), 3.4 (s), 2.5 (q), and 0.9–2.0 (m) ppm.

Anal.—Calc. for $C_{23}H_{26}F_6N_2{\cdot}2HCl{\cdot}\frac{1}{2}H_2O$: C, 52.26; H, 5.52; N, 5.30. Found: C, 52.26; H, 5.46; N, 5.20.

*6-(2-Propenyl)-6,7-dihydro-2,10-bis(trifluoromethyl)-5*H*-dibenz*[c,e]*azepine Hydrochloride* (*III*c)—Compound III*c* was similarly prepared from V (2.0 g, 0.006 mole) and allylamine (0.76 g, 0.017 mole). The mixture was extracted with ether, dried (sodium sulfate), and evaporated *in vacuo* to give a pale-yellow solid. This solid was recrystallized from carbon tetrachloride, mp 202–206°, redissolved in ether, and treated with ether–hydrochloric acid. The ether was removed *in vacuo* to give a yellow solid which was washed with carbon tetrachloride and then sublimed (110°/0.5 mm) to give 1.6 g (74%) of white crystals, mp 120° (sintering), 185–187° (clear melt); NMR: δ 7.4–7.8 (m), 5.0–6.2 (m), and 3.2–3.5 (m) ppm.

Anal.—Calc. for $C_{19}H_{16}ClF_6N{\cdot}\frac{1}{2}H_2O$: C, 54.75; H, 4.11; N, 3.36. Found: C, 55.12; H, 4.24; N, 3.13.

L-*6-(1-Benzyl-1-carboxyethyl)-6,7-dihydro-2,10-bis(trifluoromethyl)-5*H*-dibenz*[c,e]*azepine* (*III*d)—This compound was similarly prepared from V (1.0 g, 0.003 mole), L-phenylalanine (0.71 g, 0.004 mole), and sodium hydrosulfite (3.3 g, 0.018 mole). This mixture was allowed to react in methanol (20 ml) and phosphate buffer (25 ml, pH 7.6) at reflux for 12 hr. The reaction mixture was then cooled and acidified to pH 5 with 5% aqueous hydrochloric acid. The precipitate was collected and washed with 5% aqueous hydrochloric acid, water, and ether to give white crystals. The product, III*d*, was recrystallized from acetone to give 1.1 g (79%), mp 207–207.5°; NMR: δ 7.2–8.3 (m) and 3.4–4.8 (m) ppm.

[1] Melting points were determined on a Thomas-Hoover melting-point apparatus and are uncorrected. The microanalyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. NMR spectra were recorded on a Varian T-60 spectrometer, with tetramethylsilane as the internal standard. Spectral data were recorded on a Beckman IR-10 spectrometer, and UV spectra were recorded with a Beckman DB-G grating spectrophotometer.

[2] Tests were carried out in five mice infected with *P. berghei* at 40, 160, and 640 mg/kg in the screening facility of Dr. L. Rane of the University of Miami. Chicks were infected with *P. gallinaceum* fatal to 100% of untreated controls within 3–4 days. An increase of at least 100% survival time of treated animals was considered as active (7).

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

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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.