New Compounds: Synthesis of *p*-Dialkylaminoalkoxybenzoxylidides as Possible Local Anesthetics

CARLOS RODRIGUEZ-SALAZAR

Abstract □ *p*-Dialkylaminoalkoxybenzoxylidides were prepared by two methods. In the first, the potassium salt of *p*-hydroxy-2′,6′-benzoxylidide was allowed to react with dimethylaminoethyl chloride. In the second method, the sodium salt of methyl *p*-hydroxybenzoate was allowed to react with an excess of 1,2-dibromoethane; after hydrolysis, the resulting *p*-(2-bromoethoxy)benzoic acid was transformed into the acid chloride and then condensed with 2,6-dimethylaniline. Finally, the xylidide obtained was condensed with diethylamine.

Keyphrases □ *p*-(2-Dimethylaminoethoxy)-2′,6′-benzoxylidide—synthesized as possible local anesthetic □ *p*-(2-Diethylaminoethoxy)-2′,6′-benzoxylidide—synthesized as possible local anesthetic □ Anesthetics, local, potential—synthesis of *p*-dialkylaminoalkoxybenzoxylidides

Some *p*-dialkylaminoalkoxybenzoic esters possess local anesthetic activity (1–3). In the present investigation, Compounds I and II, in which the ester group has been replaced by a xylidide group, were prepared.

EXPERIMENTAL[1]

Method A—p-*Acetoxy-2′,6′-benzoxylidide*—Ninety grams (0.5 mole) of *p*-acetoxybenzoic acid was treated with 120 g (1 mole) of thionyl chloride. The acid chloride formed was condensed with 60.5 g (0.5 mole) of 2,6-dimethylaniline according to the method of Lofgren and Lundquist (4). The acetoxybenzoxylidide formed was filtered, washed with water, and recrystallized (ethanol-water), yielding 92%, mp 168–169°.

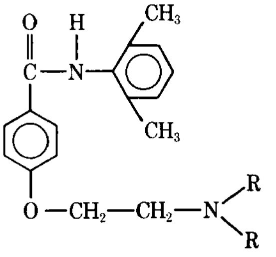
Anal.—Calc. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.00; N, 4.94. Found: C, 72.01; H, 6.15; N, 4.83.

p-*Hydroxy-2′,6′-benzoxylidide*—A mixture of 113 g (0.4 mole) of *p*-acetoxybenzoxylidide in ethanol (500 ml) and 16 g (0.4 mole) of sodium hydroxide in water (100 ml) was refluxed for 5 hr and then neutralized. The excess solvent was removed, and the solid residue was washed with water and recrystallized (ethanol-water), yielding 95%, mp 225–228°.

Anal.—Calc. for $C_{15}H_{15}NO_2$: C, 74.68; H, 6.22; N, 5.80. Found: C, 74.55; H, 6.27; N, 5.75.

p-*(2-Dimethylaminoethoxy)-2′,6′-benzoxylidide* — Twenty-four grams (0.1 mole) of *p*-hydroxybenzoxylidide was treated with 5.6 g (0.1 mole) of potassium hydroxide in methanol (200 ml), followed by 11.8 g (0.11 mole) of β-dimethylaminoethyl chloride. The mixture was refluxed for 6 hr and the excess solvent was evaporated. The resulting solid was washed with water and dissolved in dilute hydrochloric acid. The solution was treated with carbon and made alkaline with sodium hydroxide. The solid formed was washed with water and recrystallized (ethanol-water), yielding 63%, mp 147–148°.

Anal.—Calc. for $C_{19}H_{24}N_2O_2$: C, 73.07; H, 7.69; N, 8.97. Found: C, 73.16; H, 7.57; N, 8.96.



I: R = CH_3
II: R = C_2H_5

Method B—p-*(2-Bromoethoxy)benzoic Acid*—This compound was prepared from methyl *p*-hydroxybenzoate and ethylene bromide according to the method of Caldwell and Jackson (5), mp 176–180°.

p-*(2-Bromoethoxy)-2′,6′-benzoxylidide*—Seventy grams (0.285 mole) of *p*-(2-bromoethoxy)benzoic acid in 200 ml of benzene was treated with 66 g (0.54 mole) of thionyl chloride, and the mixture was heated under reflux for 4 hr. Removal of the excess thionyl chloride and solvent under reduced pressure and treatment of the residual acid chloride with 2,6-dimethylaniline gave 79 g of solid, mp 204–206°.

Anal.—Calc. for $C_{17}H_{18}BrNO_2$: C, 58.62; H, 5.17; Br, 22.97; N, 4.02. Found: C, 58.50; H, 5.19; Br, 22.79; N, 3.95.

p-*(2-Diethylaminoethoxy)-2′,6′-benzoxylidide* — Thirty-five grams (0.47 mole) of dimethylamine and 5 g of potassium iodide were added to a solution of 130 g (0.34 mole) of *p*-(2-bromoethoxy)-2′,6′-benzoxylidide in 250 ml of dimethylformamide. The mixture was refluxed for 6 hr; part of the solvent was removed under vacuum and the remaining solvent was added to cold water. After filtering, the solid was dissolved in 10% hydrochloric acid, and the solution was treated with charcoal and then precipitated with sodium hydroxide. The product was crystallized (ethanol-water) to give 100 g (87%) of white crystals, mp 143–145°.

Anal.—Calc. for $C_{21}H_{28}N_2O_2$: C, 74.18; H, 8.24; N, 8.24. Found: C, 74.14; H, 8.13; N, 8.27.

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ACKNOWLEDGMENTS AND ADDRESSES

Received May 18, 1973, from the *Departamento de Quimica Aplicadá, Facultad de Farmacia, Universidad Central de Venezuela, Caracas, Venezuela.*

Accepted for publication August 28, 1973.

Supported by Grant 336 from Consejo de Desarrollo Cientifico y Humanistico, Universidad Central de Venezuela.

The author thanks R. Pazos-Zerpa for technical assistance.

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[1] Melting points were determined with a Fisher-Johns block melting-point apparatus and are uncorrected. Elemental analyses were performed by Microanalytical Laboratory, Oxford, England. IR spectra were taken on a Perkin-Elmer model 137 spectrophotometer and were as expected.