Potential Local Anaesthetics: 2-Diethylamino-2',3',5',6'-tetramethylacetanilides

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Accepted 28 August 2002
Revised 22 July 2002
Received 22 October 2001

The synthesis of five 4'-substituted 2-diethylamino-2',3',5',6'-tetramethylacetanilides is described. The substituents vary widely in their polarity and hydrogen bonding properties.

Since the early report of the local anaesthetic activity of lidocaine [**Ia**: $R_1=R_2=R_3=H$, $Y=N(C_2H_5)_2$], more than fifty years ago, some of its derivatives have also been introduced to be useful not only as local anaesthetics but also as coronary dilators[1,2]. Recently, limited success has been reported with lidocaine in the treatment of migraine headaches[3]. Earlier, we had reported the synthesis and local anaesthetic activities of the ring methylated derivatives of lidocaine[4,5]. Results of the initial screening of these compounds and lidocaine, using the tail pinch method on mice, showed the 3',5'-dimethyl analog of lidocaine [**Ib**: $R_1=R_2=CH_3$, $R_3=H$, $Y=N(C_2H_5)_2$] to possess higher activity than lidocaine. However, the introduction of another methyl group [**Ic**: $R_1=R_2=R_3=CH_3$, $Y=N(C_2H_5)_2$] led to a significant lowering of the activity. Presently, we wish to report the synthesis of five 4'-substituted derivatives of the 3',5'-dimethyl analogs of lidocaine (**Ig-k**, Table 1), and their corresponding hydrochloride salts (**II-p**, Table 2). All the 4'-substituents differ significantly in their polarity and hydrogen bonding properties compared to CH_3 at 4' position. For the synthesis of compounds **II**, **Im** and **In** (Table 2), the corresponding anilines ($ArNH_2$) were reacted with $ClCH_2COCl$. The resulting chloroacetanilides (**Id-f**, Table 3) were prepared and reacted with diethylamine using the procedures described previously[4,5]. The diethylaminoacetanilides (**Ig-k**, Table 1) were converted to their corresponding hydrochloride salts by reacting with a solution of dry HCl gas in anhydrous ether[4,5] (**II-p**, Table 2). The aniline needed for the synthesis of **II** was obtained by Friedel-Crafts acetylation of durene. The acetyl derivative was nitrated and the nitro product reduced with tin and HCl. p-Nitroaminodurene, needed for the synthesis of **Ih** as well as **Ii**, **Ij** and **Ik** was prepared by the reduction of dinitrodurene with sodium polysulfide using the literature procedure[6]. Conversion of p-nitroaminodurene to p-fluoroaminodurene was carried out as described in the literature[7]. The reduction of **Ih** with $NaBH_4$ in 70:30 isopropyl alcohol:water mixture was a modification of the procedure used for the $NaBH_4$ reduction of ntiroanthraquinones[8], to give **Ij**. The latter was subjected to a Sandmeyer reaction to yield **Ik**.

All the chloroacetanilides and their diethylamino derivatives gave satisfactory IR and 1H NMR spectral data. The molecular formulae of the bases were derived from the respective high resolution exact mass spectral data of their hydrochloride salts (Table 2). Melting points were determined with Fisher-John or Buchii melting point apparatus and are uncorrected. The pKa measurements were made with a solution of the compounds in a 50:50 mixture of water and methanol in order to maintain a homogenous solution during titration with standard NaOH. Infrared spectral data were acquired with a FT/IR spectrometer. 1H NMR spectra were obtained with a Varian Gemini 300 MHz spec-

TABLE 1: MELTING POINTS OF THE 2-DIETHYLAMINOACETANILIDES.

Compound	1: $R_1=R_2=CH_3$ $Y=N(C_2H_5)_2$	M.P.° (range)
Ig	$R_3 = COCH_3$	89-90
Ih	$= NO_2$	101-103
Ii	$= F$	43-45
Ij	$= NH_2$	121-122
Ik	$= OH$	174-175

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trometer using $CDCl_3$ as the solvent and its trace impurity $CHCl_3$ as the internal standard. Exact mass data were obtained from the mass spectrometry facility, University of California, Riverside, CA.

Synthesis of 4-nitro-2,3,5,6-tetramethylacetophenone was initiated by slowly adding, with stirring, a solution of 8.8 g (50 mmol) of 2,3,5,6-tetramethylacetophenone in 35 ml of $CHCl_3$ to 15 ml of concentrated H_2SO_4 cooled in an ice bath. The temperature of the acid was maintained at 5° during the addition. To the cooled solution, a nitrating solution of fuming nitric acid (3 ml) in 8 ml chloroform was added dropwise. Stirring was continued and the bath temperature was slowly raised to 40° and maintained for 15 min. The reaction mixture was poured over crushed ice and the chloroform layer separated. The chloroform extract was first washed with 2.5% sodium bicarbonate solution followed by water and then dried over $CaCl_2$. Rotoevaporation of $CHCl_3$ followed by crystallization of the residue from 95% ethanol gave 7.7 g (70%) of the nitroacetophenone; m.p. 161-162.

4-Acetyl-2,3,5,6-tetramethylaniline was synthesized by slowly adding 27.3 g (0.23 mol) of granulated tin with stirring to a solution of 22.0 g (0.1 mol) of 4-nitro-2,3,5,6-tetramethylacetophenone in 100 ml of acetic acid. This was followed by the slow addition of 140 ml of concentrated HCl. The reaction mixture was stirred for another 10 h, made strongly basic with 10% NaOH solution. The crude amino ketone was crystallized from petroleum ether. Yield 9.5 g (83%); m.p. 137-138°.

Synthesis of 2-diethylamino-4'-amino-2',3',5',6'-tetramethylacetanilide (**Ij**) involved cooling a solution of 5.22 g (17 mmol) of **Ih** in 250 ml of isopropyl alcohol in an ice bath. The solution was vigorously stirred and to this 200 mg of 10% Pd on activated carbon was added. This was followed by dropwise addition (~1.2 h) of a solution of 1.0 g (25.5 mmol) of $NaBH_4$ in a 70:30 mixture of isopropyl alcohol and water. The reaction mixture was stirred overnight at room temperature. Suction filtration of the reaction mixture followed by rotoevaporation and subsequent addition of 100 ml of ice water and trituration gave a light pale solid. The product was dried in a vacuum dessicator. It weighed 4.1 g (87%), m.p. 120.5-121.5°.

Synthesis of 2-diethylamino-4'-hydroxy-2',3',5',6'-tetramethylacetanilide (**Ik**) was initiated by cooling with string

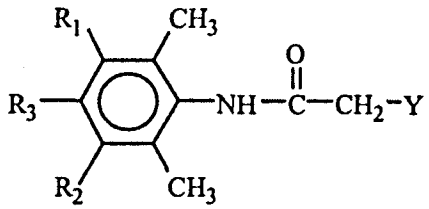

Fig. 1: 2,6-Dimethylacetanilides (I).

TABLE 2: MELTING POINTS, pKa's AND MASS SPECTRAL DATA OF HYDROCHLORIDES OF THE 2-DIETHYL AMINOACETANILIDES.

Cmpd.	I: $R_1=R_2=CH_3$; $Y=\oplus NH(C_2H_5)_2Cl\ominus$	M.P.° (range)	pK_a	Molecular formula of base	Obs. Exact mass of base	Calc. exact mass of base
Il	R_3 = $COCH_3$	102-105	7.55±0.02	$C_{18}H_{28}N_2O_2$	304.2149	304.2150
Im	= NO_2	174-175	7.25±0.02	$C_{16}H_{25}N_3O_3$	307.1888	307.1895
In	= F	148-149	7.25±0.03	$C_{16}H_{25}N_2OF$	280.1961	280.1950
Io	= $\oplus NH_3Cl\ominus$	248-250	3.50±0.02 (pK_{a1}) 7.72±0.03 (pK_{a2})	$C_{16}H_{27}N_3O$	277.2162	277.2154
Ip	= OH	250-252	7.20±0.03 (pK_{a1}) 11.5±0.2 (pK_{a2})	$C_{16}H_{26}N_2O_2$	278.1993	278.1992

TABLE 3: MELTING POINTS OF THE 2-CHLOROACETANILIDES.

Cmpd.	I: R_1=R_2=CH_3 Y=Cl	M.P.° (range)
Id	R_3 = $COCH_3$	193-194
Ie	= NO_2	207.208
If	= F	203-204

a solution of 1.39 g (5 mmol) of Ij in 15 ml of 10% HCl in an ice-salt bath to ~0°. To this, a solution of 0.38 g (5.5 mmol) $NaNO_2$ in 10 ml water was slowly added. Another 30 ml of ice cold HCl was added 15 min after the addition of $NaNO_2$ solution. The reaction mixture was allowed to warm without the cooling bath. Bubbling was noticed at ~20°. The temperature was slowly raised to 95° by warming in a water bath. The solution was neutralized with a mixture of solid $NaHCO_3$ and saturated $NaHCO_3$ solution. The organic product was extracted with CH_2Cl_2, washed with water and dried over Na_2SO_4. Removal of solvent gave 1.04 g crude product which was purified by column chromatography over 30 g alumina using 90:10 CH_2Cl_2:hexane followed by CH_2Cl_2 and then increasing proportions of isopropyl alcohol in CH_2Cl_2 as the solvents. Fractions that gave residues with m.p. close to each other were combined. The total weight of fractions of m.p. 174-175° (represented 40.3% yield).

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Spectrophotometric Method for the Determination of Tobramycin in Pharmaceutical Formulations

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Accepted 28 August 2002

Revised 22 July 2002

Received 7 March 2002

A sensitive and accurate spectrophotometric method for the quantitative determination of tobramycin in either pure form or in injections is proposed. The method is based on the development of a green coloured product with 3-methyl-2-benzothiazolinone hydrazone hydrochloride and ferric chloride having an absorption maximum at 645 nm. Beer's law is obeyed in the concentration range of 50-500 μg/ml. The optimum reaction conditions and other analytical parameters are statistically evaluated.

Tobramycin (TM) is a simple aminoglycoside antibiotic with an extended spectrum of activity against gram negative and aerobic bacilli[1]. It is official in Indian Pharmaco-

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