DEUTERATION OF THE RACEMATE AND THE (2S)-(+)-ENANTIOMER OF THE ANTIARRHYTHMIC AGENT DISOPYRAMIDE, 4-DIISOPROPYLAMINO-2-(2-PYRIDYL)-2-PHENYLBUTYRAMIDE

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SUMMARY

Deuteration of disopyramide, 4-diisopropylamino-2-(2-pyridyl)-2-phenylbutyramide, was accomplished in an excess of $^{2}H_2SO_4$ at 125-135°C. Incorporation of 2-4 atoms of deuterium occurs with 65% recovery of disopyramide. At higher temperatures (150°C) greater incorporation of deuterium occurs, but substantial decomposition reduces the recovery of disopyramide to 25%.

Key Words: disopyramide, deuterium exchange

INTRODUCTION

Disopyramide (1), 4-diisopropylamino-2-(2-pyridyl)-2-phenylbutyramide,[1] is an orally effective, quinidine-like agent used in the treatment of cardiac dysrhythmias in the United States it has gained prompt acceptance. Interest in its pharmacokinetic behavior, metabolic fate and scope of therapeutic applications has accompanied its wide use.[4-7] Although it has been shown to have electrophysiologic properties similar to structurally unrelated quinidine, and to produce fewer adverse reactions, undesirable side effects have been reported, including those related to its anticholinergic properties, negative inotropic activity and congestive heart failure.[3,8] Some differences in the disposition of the enantiomers of disopyramide have been reported in dogs[9] and rats[10] suggesting there could be differences in some of the pharmacologic properties of the enantiomers of the drug, as well.

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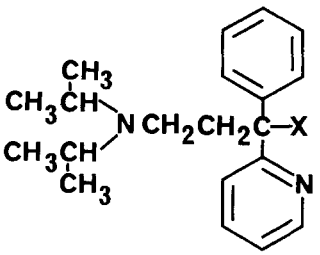
In order to further study the metabolic disposition of racemic disopyramide and its enantiomers,[11] a suitable method for stable isotope labelling was sought. Although synthesis of ^{14}C-radiolabelled disopyramide has been reported,[12] and multi-step syntheses of disopyramide-^{13}C,^{15}N (from benzyl cyanide-^{13}C,^{15}N) and disopyramide perdeuterated in the N-isopropyl groups have appeared recently,[13] easily obtained stable isotopically labelled parent drug and its enantiomers seemed to offer several potential applications. Consistent with these potential uses, we sought a simple procedure for incorporation of deuterium. In this paper preparation of deuterated racemic disopyramide and its (2S)-(+)-enantiomer, based of a facile exchange in deuterated sulfuric acid is reported.



1 X = $CONH_2$

2 X = H

3 X = CN

RESULTS AND DISCUSSION

Initial deuterium exchange experiments were monitored by nmr while varying the conditions of sulfuric acid concentration, time and temperature. Under conditions of $^2H_2SO_4$, at 25 to 100% in deuterated water, at 25-90°C, almost no exchange was detected by nmr over a period of three to five hours. The signals of the aromatic protons [2 broad signals at 7.43 δ (2 protons), W_h (width at half-height) = 12 Hz, and at 7.77 δ (3 protons), W_h = 10 Hz] and of the pyridyl protons [signals at 8.30 δ (2 protons) and at 8.83 δ (2 protons)] were monitored. In $^2H_2SO_4$ (98% deuterium) at 120-130°C significant exchange occurred in 4-5 hours. In $^2H_2SO_4$ (98% deuterium) at 145-155°C most of the aromatic portion of nmr signal had disappeared in 4-5 hours; however, only 25% recovery of disopyramide was realized, and in some runs even less. CI-Mass spectral analysis of the enchanged disopyramide showed ions at m/e 342, 343, 344, 345 amu, corresponding to

incorporation of 2, 3, 4 and 5 atoms of deuterium [QM (quasimolecular ion) for disopyramide = 340 amu] in the relative ratio of 30:70:100:23. By TLC, the crude product was contaminated with material that showed ions at m/e 298 to 303 amu, quasimolecular ions with deuterium incorporation corresponding to loss of the carboxamide group to produce 2 in the acid catalyzed deuteration process. Exchange on the (2S)-(+)-enantiomer of disopyramide in $^2H_2SO_4$ (98% deuterium) at 125°C provided incorporation of an average of 2 to 3 atoms of deuterium into the aromatic ring with 65% recovery. As expected, no racemization occurred as determined by optical rotation measurements.

Attempts to use deuterated trifluoroacetic acid for the exchange were unsuccessful. At 100-125°C (sealed container), no deuterium was incorporated and significant dehydration occurred producing nitrile 3 (QM = 322 amu). A similar dehydration of disopyramide has recently been reported.[14]

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane or sodium 3-(trimethylsilyl)-propanesulfonic acid as internal standard. Chemical ionization mass spectra were obtained on a Biospec quadrupole mass spectrometer using methane (0.5 torr) as reagent gas. Optical rotations were recorded on a Jasco DIP-4 digital polarimeter.

Deuteration of Racemic 4-Dilsopropylamino-2-phenyl-2-(2-pyridyl)butyramide--Racemic disopyramide (1) (1.29 g, 3.81 mmol), was dissolved in 5 ml of $^2H_2SO_4$ (98% deuterium - Stohler Isotope Chemicals) and heated at 150°C while stirring for 4.5 h. The acidic solution darkened considerably upon heating. In the nmr spectrum of the reaction mixture before heating (in $^2H_2SO_4$), multiplets were observed at 7.43 δ (2 protons) [W_h (width at half-height) = 12 Hz] and 7.77 δ (3 protons) (W_h = 10 Hz) for the aromatic protons and at 8.30 δ (2 protons), broadened triplet, J ≃ 6-7 Hz and 8.83 δ (2 protons), doublet, J ≃ 6-7 Hz, for the pyridyl protons. After 4.5 h the two upfield multiplets had nearly disappeared. In the nmr spectrum of the product of deuterium exchange (in $CDCl_3$),

the singlet at 7.28 δ was reduced in intensity by about 80% compared to disopyramide starting material. The reaction mixture was diluted with water and adjusted to the pH 11 with 12N NaOH. The aqueous solution was extracted with Et_2O (5 x 80 ml) and EtOAc (5 x 80 ml). The combined organic extracts were washed with water (3 x 100 ml), dried (Na_2SO_4) and evaporated affording 840 mg (65%) of a light yellow oil. Crystallization from 2.5 ml of cyclohexane afforded 393 mg (30%) of white crystals, mp 79.5-81°C. CI-mass spectrum: 345, 344, 343, 342 amu (23:100:70:30) indicating greatest incorporation of 4 atoms of deuterium (344 amu) and lesser amounts of disopyramide with 3, 2 and 5 deuterium atoms.

Deuteration of (2S)-(+)-4-Diisopropylamino-2-phenyl-2-(2-pyridyl)butyramide--(2S)-(+)-Disopyramide[11] (1.29 g, 3.81 mmol) was dissolved in 5 ml of $^2H_2SO_4$ (98% deuterium - Stohler Isotope Chemicals). The mixture was heated at 150°C for 4.5 h. Subsequent workup as described above afforded 1.14 g (88%) of a light yellow oil which was crystallized from cyclohexane. Repeated crystallization from hexane afforded 331 mg (26%) of white crystals, mp 81-82°C [lit.[11] mp 82-84°C (nondeuterated)]; $[\alpha]_D^{25}$ = +18.2° (c 1.0 MeOH); ir (KBr) 2273 cm^{-1} (C-D stretch). CI-mass spectrum: 346, 345, 344, 343, 342 (11:67:100:84:46).

In a subsequent run from 5.00 g (12.7 mmol) of (2S)-(+)-disopyramide in 15 ml of $^2H_2SO_4$ heated at 125°C, 5 h, 3.23 g (65%) of deuterated (2S)-(+)-disopyramide was obtained, mp 82-84°C. CI-mass spectrum; 345, 344, 343, 342, 341, 340 amu (16:67:100:100:50:16) indicating greatest incorporation of 2 and 3 atoms of deuterium (342 and 343 amu).

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