SYNTHESIS OF DEUTERIUM LABELLED ZOMEPIRAC

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SUMMARY

A simple synthetic procedure has been developed for the preparation of deuterated zomepirac. The deuterium was incorporated into the aromatic ring which is a metabolically stable position.

Key words: zomepirac deuterium exchange

INTRODUCTION

Zomepirac sodium (1) is a new nonnarcotic analgesic agent chemically similar to tolmetin. It has been evaluated for use as an analgesic possessing the efficacy of morphine but devoid of undesirable narcotic-like properties and is approved for the relief of mild to moderately severe pain as demonstrated in clinical trials (1-8). The pharmacokinetics and metabolism of 1 in man and animals have been reported (9-12) using ^{14}C-labeled zomepirac (9,10,12). Gas chromatography (GC) (10) and high performance liquid chromatography (HPLC) (11,13) methods of analysis have been used in the determination of zomepirac levels in biological samples. We have directed our efforts towards developing a new method of analysis for this drug. Gas chromatography mass spectrometry (GCMS) coupled with selected ion monitoring is used increasingly in drug research because of its high sensitivity and specificity. In this technique, stable isotope-labeled carriers are ideal internal standards, especially for the measurement of trace amounts of drug in biological samples (serum, saliva, urine, etc). Zomepirac is a pyrrole structure with a side chain containing a benzene ring. There are four hydrogens on the

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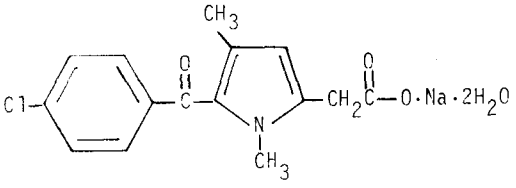
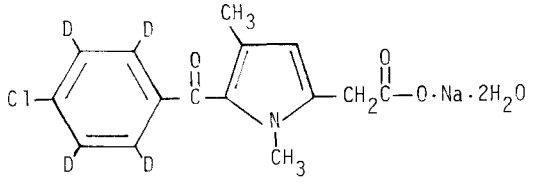
aromatic ring that can be readily replaced by deuterium prior to substitution of the aroyl group on the pyrrole ring. We undertook the synthesis of zomepirac-d_4 (2) and this is reported here.



zomepirac sodium

1



zomepirac sodium-d_4

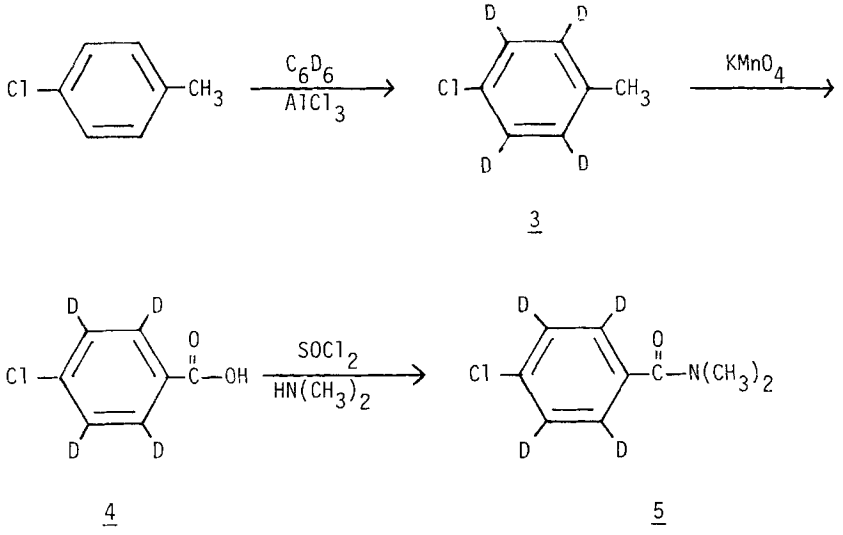
2

RESULTS AND DISCUSSION

Scheme 1 shows the reaction sequence used to obtain p-chloro-N,N-dimethylbenzamide-d_4 (5). The exchange reaction between benzene-d_6 and p-chlorotoluene proceeds nicely in the presence of anhydrous aluminum chloride according to the methods described by Long et al. (14). Using equimolar quantities of C_6D_6 and p-chlorotoluene the calculated exchange that should occur using successive portions of fresh C_6D_6 is as follows: first exchange 60%; second 84%; third 93%; fourth 97%; fifth 99%. After the fifth exchange reaction with fresh C_6D_6 the product (3) was found by mass spectrometry to approach theoretical (>98% deuterium labelling of the aromatic ring). The oxidation of 3 using $KMNO_4$ is not particularly efficient. The oxidation occurs in higher yield using α,p-dichlorotoluene. Unfortunately α,p-dichlorotoluene in the exchange reaction

gives largely the Friedel-Crafts reaction product with C_6D_6. The exchange reaction does not occur with p-chlorobenzoic acid or its N,N-dimethylamide. This result is consistent with the observations of Long et al. (14) where aromatic compounds containing oxygen and nitrogen substituents did not readily undergo the exchange reaction.

Scheme 1



Scheme 2 shows the reaction sequence to obtain zomepirac-d_4. This scheme is identical to the synthesis of zomepirac first described by Carson and Wong (15). In our experience most of the pyrrole compounds and especially 6, were readily oxidized to deep coloured materials. If storage of intermediates was necessary they were kept cold under nitrogen. The product 2 was obtained in pure form with the degree of deuterium labelling essentially the same as that of the p-chlorotoluene-d_4 (3). Tables 1 and 2 compare the spectroscopic data for the deuterium analog to that of a reference sample of zomepirac.

Scheme 2

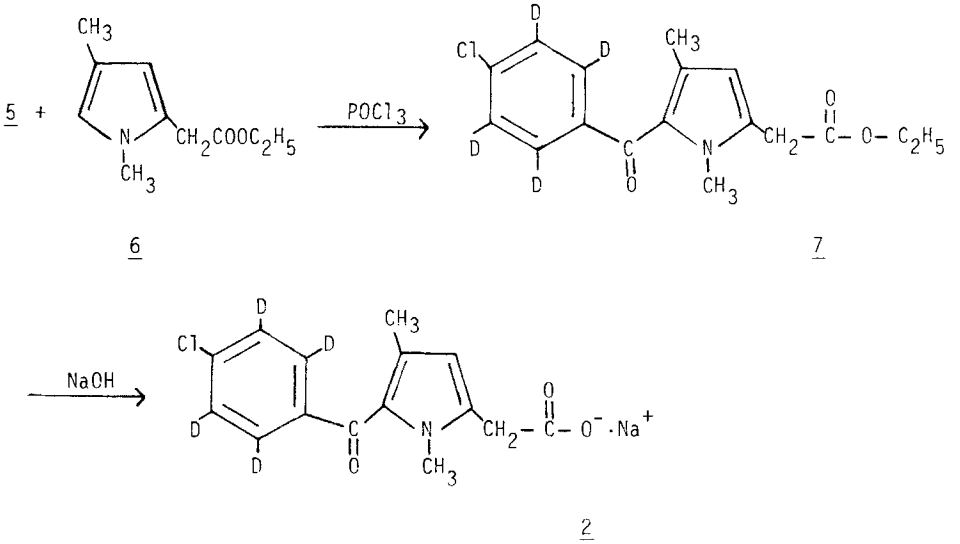


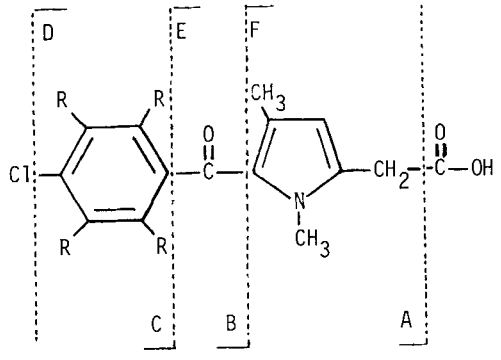
Table 1

Comparison of spectroscopic data of reference zomepirac and synthesized zomepirac-d_4 (free acid forms)

	Zomepirac	Zomepirac-d_4
UV	λmax_1 330 nm (ε = 1.35 x 10^4)	λmax_1 330 nm (ε = 1.46 x 10^4)
	λmax_2 261 nm (ε = 1.03 x 10^4)	λmax_2 261 nm (ε = 1.10 x 10^4)
IR (KBr disc) νmax	2925 cm^{-1} (b,s,-OH), 1705 (s,C=O) 1380 and 1220	2925 cm^{-1}, 1700, 1365, 1220
NMR Chemical Shift (δ)		
Benzenoid	7.38 - 7.75 (d,d) J = 9H_z	----------
Pyrrole Ring Proton	5.98 (s)	5.98 (s)
CH_2 - COOH	3.75 (s)	3.75 (s)
N - CH_3	3.71 (s)	3.71 (s)
C - CH_3	1.75 (s)	1.75 (s)

Table 2

Comparison of the EI mass spectra of zomepirac and zomepirac-d_4



zomepirac (R = H)

zomepirac-d_4 (R = ^{2}H)

m/z (%)		Assignment	
Zomepirac	Zomepirac-d_4	Zomepirac	Zomepirac-d_4
246 (100)	249 (100)	A - H	A - D
247 (62)	251 (88)	A	A
211 (51)	214 (42)	A - H - Cl	A - D - Cl
136 (34)	136 (43)	E - CO_2	E - CO_2
108 (21)	108 (18)	F - CO_2	F - CO_2
111 (17)	115 (18)	C	C
139 (7)	143 (8)	B	B

EXPERIMENTAL

All the melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The UV spectra (Na salts in H_2O) were recorded on a Beckman Model-25 spectrophotometer. The IR spectra were obtained with a Unicam SP-1000 spectrophotometer. Mass spectra were determined using a

Mat 111 GCMS and a glass column packed with 3% Dexsil-300. The NMR spectra were recorded at the Chemistry department of UBC using a Bruker WP-80 instrument; the acid forms were dissolved in $CDCl_3$ with tetramethylsilane added as reference.

Deuteration of p-chlorotoluene

In a mixture of 12.6 g (0.1 mole) of p-chlorotoluene and 8.4 g (0.1 mole) of C_6D_6, 0.5 g of anhydrous aluminum chloride was added. The mixture was refluxed at 90°C for 0.5 h to permit the exchange to reach equilibrium. The mixture was fractionated to remove the benzene. Another 8.4 g (0.1 mole) of fresh C_6D_6 was added and refluxed at 90°C for another 0.5 h and the benzene removed as before. This procedure was repeated three additional times whereby more than 98% of the hydrogen on the benzene ring of the chlorotoluene molecule was replaced by deuterium. When the fifth exchange was completed and the benzene removed by fractionation, the residue (a mixture of p-chlorotoluene and aluminum chloride) was used directly in the next step because the separation of p-chlorotoluene-d_4 from aluminum chloride is troublesome.

Synthesis of p-chlorobenzoic acid-d_4 (4)

The residue of the previous step was transferred cautiously to a 500 ml 3-neck flask equipped with a reflux condenser and a stirrer. Water (250 ml) and 15 g of $KMnO_4$ were added. The mixture was stirred and refluxed until the $KMnO_4$ color disappeared (about 2 h). An additional 7.5 g of $KMnO_4$ was added and refluxed again until the permanganate color disappeared again (approx. 2 h). Finally, a third 7.5 g of $KMnO_4$ was added and refluxing continued until the permanganate color disappeared once again (2-4 h). Steam distillation was performed to remove the unreacted p-chlorotoluene-d_4. The hot contents of the flask were filtered from the manganese dioxide with suction and the residue was washed with two 125 ml portions of hot water. The filtrate was acidified with concentrated HCl. A white precipitate which formed was filtered off, washed with water and dried to give 6.4 g of p-chlorobenzoic acid-d_4 (40% yield based on p-chlorotoluene) mp 238-239°. (Literature (18) p-chlorobenzoic acid, mp. 238-239°C).

p-Chloro-N,N-dimethylbenzamide-d_4 (5)

p-Chlorobenzoic acid-d_4 (8.6 g) and 10 g of $SOCl_2$ in a 50 ml flask, protected from atmospheric moisture by a drying tube was refluxed for 1 h until all the solid was dissolved. The equipment was rearranged to remove the excess thionyl chloride by distillation. The acid chloride was treated cautiously with about 20 parts of a solution of 25% dimethylamine (the reaction was vigorous and considerable heat was produced). The solution was extracted with three 40 ml portions of CH_2Cl_2. The combined CH_2Cl_2 fractions were evaporated under vacuum to give a light brown semisolid. The purity of the product was checked by GCMS and found to be greater than 95% pure.

Ethyl 1,4-dimethylpyrrole acetate (6)

The procedure used was that of Carson and Wong (15). The product was isolated as a colorless oil bp 73-80°, 0.03-0.04 mm, (literature (15) 82-90°, 0.025 mm). The product was very easily oxidized and therefore stored in the cold under nitrogen.

Vilsmeier Aroylation (17) of (6)

The ethyl ester of zomepirac-d_4 (7) was synthesized by Vilsmeier Aroylation of 6. The procedure used was again similar to that reported by Carson and Wong (15).

Saponification of ester (7)

Ester (7), 22 g, was refluxed for 1 1/2 h with 13.6 g of sodium hydroxide in 200 ml of water. Upon acidification, a yellowish precipitate was formed which when filtered off and air-dried gave 15.7 g of the acid form of zomepirac-d_4. Recrystallization with isopropanol gave light yellow needle-like crystals, mp 178-179°C.

Zomepirac-d_4 sodium salt

To zomepirac-d_4 dissolved in an adequate amount of warm isopropanol was added an equimolar amount of concentrated solution of sodium hydroxide. Upon cooling yellowish crystals were deposited and collected by filtration. Recrystallization with methanol gave pale needle-like crystals mp 302-303°C (decomp.) (yield 60%). (Reference zomepirac sodium m.p. 303-305°C).

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