# SYNTHESIS OF TRITIUM LABELED ZOMEPIRAC

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## SUMMARY

Tritium labeled zomepirac with a specific activity of 85 Ci/mmol was prepared by selective alkylation of the penultimate desmethyl precursor using methyl iodide-$^{3}H_{3}$. The alkylation reaction was explored using various bases and solvent media.

Keywords: zomepirac, tritium, synthesis, stability, methyl iodide, alkylation.

## INTRODUCTION

Zomepirac sodium (1, ZOMAX®***) is a non-narcotic analgesic drug used in the treatment of mild to moderately severe pain. The aspects of the metabolism and pharmacology of this compound have been previously

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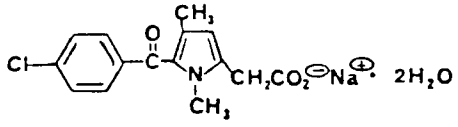
published[1-5] as well as the synthesis of the major metabolite[6]. In addition, the synthesis of zomepirac labeled with deuterium in the chlorobenzoyl group has recently been described.[7]

During the course of ongoing research a sample of tritiated zomepirac was required for use in receptor site studies. The nature of the studies necessitated that the radiolabel be chemically stable and have a high final chemical and radiochemical purity. The minimum acceptable specific activity was considered to be in the range of 60-80 Ci/mmol. Satisfactory introduction of the label and attainment of the required specific activity by catalytic exchange or reduction methods were precluded by the structure of the compound. The procedure used in this work involved synthesis of the N-desmethyl precursor (2) followed by alkylation with high specific activity tritium labeled methyl iodide.

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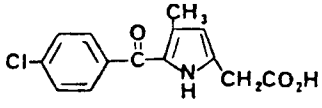


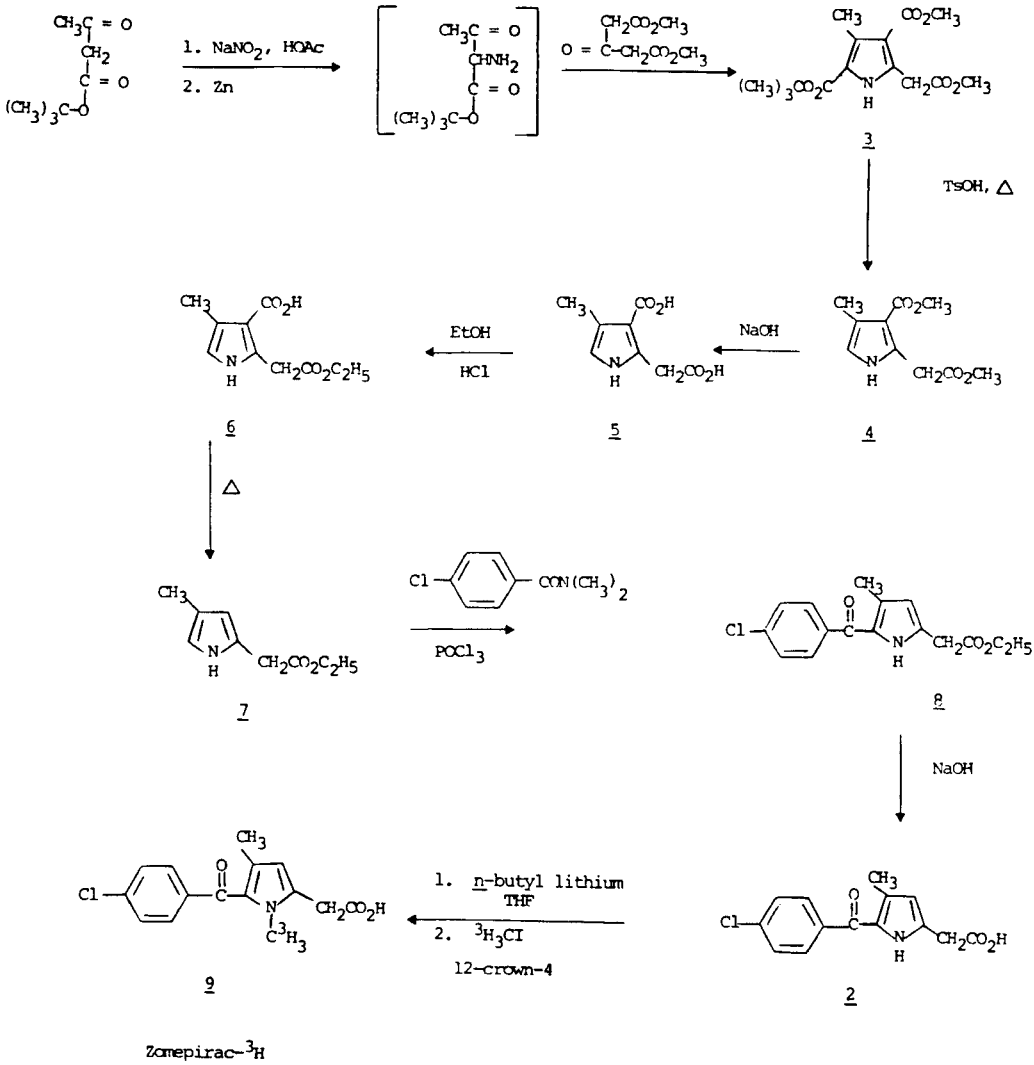

2

## RESULTS AND DISCUSSION

The synthesis of aroylpyrrole acetate 2 and the subsequent alkylation reaction are outlined in scheme I. The alkylpyrrole dicarboxylate 4 was prepared by extension of the Knorr pyrrole synthesis[8] using the procedure of Treibs and Hintermeier.[9]

Nitrosation of tert-butyl acetoacetate proceeded smoothly in glacial acetic acid at 20°C. This was reduced to the amine in situ with zinc powder and condensed with dimethyl 1,3-acetonedicarboxylate to give the triester (3). Decarbalkoxylation of 3 was carried out at 170°C in the presence of a catalytic amount of p-toluenesulfonic acid. This material

Scheme I


1. NaNO2, HOAc
2. Zn
TsOH, Δ
NaOH
EtOH
HCl
Δ
POCl3
1. n-butyl lithium
THF
2. 3H3CI
12-crown-4
NaOH
3
4
5
6
7
8
2
9
Zomepirac-3H

was converted to 6 using procedures similar to those previously described for the N-methylated and desmethyl benzoyl substituted derivatives [5, 10]. Hydrolysis of 4 to the diacid with aqueous sodium hydroxide was followed by selective monoesterification with ethanolic hydrogen chloride to afford monoester 6. Thermal decarboxylation of 6 followed by vacuum distillation gave ester 7. This pyrrole acetate was condensed with N,N-dimethyl-4-chlorobenzamide using phosphorous oxychloride in dichloroethane to give compound 8. Saponification with ethanolic sodium hydroxide provided the desmethyl zomepirac (2).

Alkylation of 2 was carried out by treatment with two equivalents of n-butyl lithium in THF at -78°C to give a reddish colored solution of the dianion. Addition of two equivalents of 12-crown-4 followed by two equivalents of tritiated methyl iodide and heating for one day at 100°C gave a 10 - 20% purified chemical yield of zomepirac-$^{3}$H (9). The relatively slow N-methylation was the sole alkylation reaction, giving acid 9 cleanly after purification by preparative tlc. The isolated product had a specific activity of 85 Ci/mmol and a radiochemical purity greater than 98%.

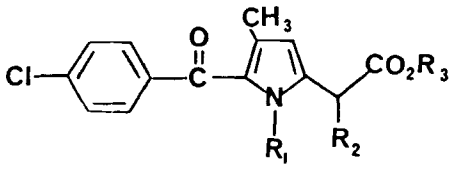
Numerous reaction conditions were examined in an effort to improve both the yield and rate of the alkylation reaction. Some of the results are listed in Table I. When a polar solvent such as DMF was used for the alkylation, the dianion of 2 was immediately esterified to 10 upon the addition of methyl iodide. The ester was then alkylated at the pyrrole nitrogen and/or the carbon adjacent to the carboxylate group to give a mixture of products 11, 12 and 13.

Esterification, however, was not significant in less polar solvents such as THF. This effect is presumably due to close ion pair formation between the counterion and carboxylate group which prevents ionization and the subsequent esterification reaction[11]. Methylation in THF, therefore, selectively gave only the desired N-alkylated product but

TABLE I: Alkylation of 2 with methyl iodide using various bases and solvents.

| base | solvent[a] | main products[b,c] |
|---|---|---|
| potassium isopropoxide | dimethylformamide | 10 |
| n-butyl lithium | dimethylformamide | 10 ,11, 12, 13 |
| n-butyl lithium | tetrahydrofuran/12-crown-4 | 9 |
| n-butyl lithium | glyme/12-crown-4 | trace of 9 |
| n-butyl lithium | diglyme/12-crown-4 | no reaction |
| n-butyl lithium | dioxane/12-crown-4 | no reaction |
| n-butyl lithium | tetrahydrofuran | 9 |
| n-butyl lithium-potassium hydride | tetrahydrofuran | 9 |
| potassium hydride | tetrahydrofuran | trace of 9 |
| benzyltrimethyl-ammonium hydroxide | tetrahydrofuran | 11, 12, 13 |
| sodium hydroxide | methylene chloride/water/benzyltriethylammonium chloride | 10 |
| methyl magnesium bromide | tetrahydrofuran | no reaction |

a. Products were identified by thin-layer chromatography on silica gel GF with chloroform-acetic acid (95:5, v/v) as the solvent system.
b. Most reactions also gave unidentified polar and non-polar impurities.
c. Scout reactions were carried out with 0.10 mmol 2, 0.20 mmol base, and 0.10 mmol methyl iodide in 5 ml solvent. Reactions were carried out in sealed ampules or stoppered flasks. Excess methyl iodide (0.05 mmol) was required for full reaction to be observed due to small volatility losses in the stoppered flasks.



| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 10 | H | H | $CH_3$ |
| 11 | $CH_3$ | H | $CH_3$ |
| 12 | H | $CH_3$ | $CH_3$ |
| 13 | $CH_3$ | $CH_3$ | $CH_3$ |
| 14 | $CH_3$ | H | $CH_2CH_3$ |
| 15 | H | $CH_3$ | $CH_2CH_3$ |
| 16 | $CH_3$ | $CH_3$ | $CH_2CH_3$ |

required up to three days for complete reaction. No reaction was observed in diglyme or dioxane and the rate of N-methylation in glyme was much slower than that observed in THF. As expected, the nature of the counterion also influenced the rate of the esterification reaction. In THF the di-lithium salt of 2 reacted slowly to give only the N-methylated product. The di-potassium salt reacted much slower under similar conditions. Quaternary ammonium salts of 2 reacted to give esterification and alkylated products 11, 12, and 13. Experiments employing methyl tosylate or methyl sulfate as the alkylating agent showed decreased selectivity under the same reaction conditions. Methyl sulfate proved to be more reactive, providing alkylated products at a lower temperature than methyl iodide. Treatment of the di-lithio salt of 2 with methyl sulfate gave a small amount of 9 and other esterified alkylated products, while the potassium and benzyltrimethylammonium salts readily provided esterification and alkylation.

Selective N-methylation of ethyl ester 8 was also attempted using a wide variety of bases in both polar and nonpolar solvents. Reaction with methyl iodide gave primarily C-alkylation and product 15 was isolated by

preparative thick-layer chromatography and identified by NMR and MS.* Varying the counterion had no effect upon the formation of the C-alkylated product (15). The lithium, sodium, potassium, tetrabutylammonium, benzyltrimethylammonium, and thallium salts all gave similar results. Addition of 18-crown-6 had no observable effect on the reaction outcome. Changing the solvent polarity over the range of ethers, alcohols, and dipolar aprotic solvents also did not alter the regioselectivity. When methyl sulfate was employed as the alkylating agent facile regioselective N-methylation was observed using sodium hydride and DMF.

## EXPERIMENTAL SECTION

Preparation of tritiated methyl iodide and the alkylation reaction were carried out by Amersham Corp., Arlington Heights, IL. Specific activities and concentrations were determined on a Searle Isocap/300 liquid scintillation counter. Radioscans were taken on a Varian-Berthold Series 6000 thin-layer scanner. Dimethyl 1,3-acetonedicarboxylate, 4-chlorobenzoyl chloride and tert-butyl acetoacetate were obtained from Aldrich Chemical Co. The 4-chloro-N,N-dimethylbenzamide was prepared by the dropwise addition of a 40% aqueous solution of dimethylamine to 4-chlorobenzoyl chloride at 0°C. The resulting mixture was stirred for one hour and filtered. The filter cake was dried, dissolved in methylene

*Spectroscopic analysis of the acid obtained upon hydrolysis of 15 with sodium hydroxide gave the following data:
NMR: (3 mg/50 µl DMSO-$d_6$, δ in ppm from TMS) δ 1.38 (3H, doublet, $CH_3CH$), 1.96 (3H, singlet, $CH_3$-C), ~3.75 (1H, quartet, $CH_3CH$), 5.98 (1H, singlet, pyrrole H), 7.6 (4H, singlet, aromatic H), 11.38 (1H, broad singlet, NH).
Mass Spectrum: (chemical ionization with methane) m/z 292 $(M+H)^+$, m/z 248 $(M-CO_2)+H^+$.
IR: ($CHCl_3$) diagnostic bands at 1720 $cm^{-1}$ ($-CO_2H$) and 1690 $cm^{-1}$ (ketone).
UV: (methanol) $\lambda_{max}$ 325 and 250 nm.

chloride, and filtered. The filtrate was concentrated to dryness and the tan colored crystalline product recovered in an 80% yield (m.p. 49 - 52°C, uncorrected).

Methyl 4-Methyl-3-methoxycarbonyl-1H-pyrrole-2-acetate (4)

Compound 4 was prepared on a 0.5 mole scale according to the procedure outlined in reference 9. The product was recrystallized from ethanol to give an off-white crystalline solid with a melting point of 89 - 92°C (uncorrected).

3-Carboxy-4-methyl-1H-pyrrole-2-acetic acid (5)

A suspension of 50.4 g (0.239 mol) of 4 in 0.5 l of 6N sodium hydroxide was heated in an oil bath at 80 - 85°C for 3.5 hours. The resulting solution was cooled and slowly acidified to pH 3 with hydrochloric acid solution. A tan colored precipitate was collected by suction filtration and air-dried for two days to give 37.9 g (87%) of a crystalline solid with a melting point of 188 - 190°C (dec.). Thin layer chromatography on silica gel with a chloroform - acetic acid (9:1, v/v) solvent system showed the material to be a single component ($R_f$ 0.55).

Ethyl 3-Carboxy-4-methyl-1H-pyrrole-2-acetate (6)

A solution of 37.9 g (0.207 mol) of 5 in 350 ml of 1% dry hydrogen chloride in ethanol was stirred at room temperature for two hours. The mixture was cooled and a solid precipitate collected by suction filtration. The filtrate was concentrated to dryness on a rotary evaporator and the residue combined with the filter cake and recrystallized from ethanol. The product was collected and dried *in vacuo* at 40°C to give 34 g (78%) of a tan solid with a melting point of 174 - 175°C (dec.). Thin layer chromatography on silica gel with chloroform - acetic acid (9:1, v/v) showed a single spot ($R_f$ 0.83).

Ethyl 4-Methyl-1H-pyrrole-2-acetate (7)

A 34 g (0.161 mol) sample of 6 was heated at 240°C under a nitrogen gas atmosphere for 5.5 hours. The reaction was vacuum distilled to give 17 g (63%) of a pale-green colored liquid (bp. 60 - 110°C, 0.5 mm). Thin layer chromatography on silica gel with ethyl acetate-cyclohexane (1:4, v/v) showed the material to be a single component ($R_f$ 0.34).

Ethyl 5-(4-Chlorobenzoyl)-4-methyl-1H-pyrrole-2-acetate (8)

Phosphorus oxychloride (16 g, 0.104 mol) was added to a solution of 18 g (98 mmol) of 4-chloro-N,N-dimethylbenzamide in 35 ml of 1,2-dichloroethane. This mixture was heated at reflux temperature for 1.25 hours. To this mixture was added 17 g (0.102 mol) of 7 dissolved in 35 ml of 1,2-dichloroethane and the reaction heated at reflux temperature for an additional 1.25 hours. The reaction was cooled to 25°C and a solution of 68 g (0.83 mol) sodium acetate in 100 ml water was added and the resulting mixture heated for 15 min. at reflux temperature. The reaction was poured over ice and extracted with methylene chloride. The organic layer was separated, washed with a saturated solution of sodium chloride, and dried over anhydrous magnesium sulfate. The mixture was filtered and evaporated to dryness on a rotary evaporator. The residue was chromatographed on a silica gel column using a cyclohexane - ethyl acetate (1:1, v/v) solvent system. The fractions containing product (tlc) were collected and evaporated to dryness. The material was recrystallized from isopropanol to give 11.3 g (36%) of a crystalline solid; melting point 125-126°C, mass spectra: m/z 306 $(M+H)^+$.

5-(4-Chlorobenzoyl)-4-methyl-1H-pyrrole-2-acetic acid (2)

A suspension of 8 (11.3 g, 37.0 mmol) in 50 ml of 1N sodium hydroxide was heated at reflux temperature for one hour. The solution was cooled and poured into 6N hydrochloric acid solution. The precipitate was

filtered and dried in vacuo at 40°C to give a quantitative yield of off-white crystalline material; tlc: silica gel, chloroform-acetic acid (98:2, v/v, $R_f$ 0.28).

5-(4-Chlorobenzoyl)-1,4 dimethyl(1-$^3H_3$)-1H-pyrrole-2-acetic acid (9)

A solution of N-desmethyl zomepirac (2, 36 μmoles) dissolved in 1.2 ml of anhydrous tetrahydrofuran, prepared in a clean, dry 2 ml glass reaction vessel containing a magnetic stirring bar, was cooled in a dry ice-acetone bath. To this was added a solution of (72 μmoles) n-butyl lithium dissolved in 0.05 ml of hexane in a dropwise manner with vigorous stirring and under a nitrogen atmosphere. The solution turned orange in color and 72 μmoles of 12-crown-4 (Aldrich Chem. Co.) was added to the reaction. Tritiated methyl iodide (10 Ci, 85 Ci/mmol) was vacuum transferred into the reaction flask which was sealed and heated at 100°C for eight hours. The solvent was evaporated in vacuo and the residue (4 Ci) partitioned between 0.7 ml of chloroform and 0.3 ml of 1N hydrochloric acid. The organic layer was separated, dried over sodium sulfate and applied to a 20 x 20 cm x 2000 μm silica gel preparative thick layer plate. The plate was eluted with chloroform containing 1% glacial acetic acid. The band corresponding to zomepirac-$^3H$ ($R_f$ 0.29, visualized under UV light) was scraped from the plate and the silica gel extracted three times with 15 ml of methanol. The solvent was evaporated and the tlc purification procedure repeated two additional times. The isolated residue was partitioned between 0.5 ml of chloroform and 0.5 ml 1N hydrochloric acid. The organic layer was separated, dried over sodium sulfate and the solvent evaporated. Labile tritium was removed by refluxing the product in a 15% solution of 1N sodium hydroxide dissolved in ethanol. The solvent was evaporated and the aqueous residue acidified with hydrochloric acid to pH 2. The aqueous layer was then extracted with chloroform and the organic layer separated, dried over

sodium sulfate and the solvent evaporated. A 50 mCi portion of the product was dissolved in an ethanol-water (9:1) mixture and stored at 0°C at a radioactive concentration of 4.5 mCi/ml.

## ANALYSIS AND STABILITY

Zomepirac prepared from trial runs using intermediate 2 as the starting material was characterized spectroscopically. IR: (0.3% in KBr) 1730 $cm^{-1}$, 1700 $cm^{-1}$, 1610 $cm^{-1}$; UV: (1 mg/50 ml $CH_3OH$) 253 nm ($\epsilon$12,600), 325 nm ($\epsilon$13,800); NMR: (DMSO-$d_6$, $\delta$ in ppm from TMS) $\delta$ 1.7 (3H, singlet, $CH_3$-C), 3.5 (2H, singlet, $CH_2$-), 3.7 (3H, singlet, $CH_3$-N), 5.9 (1H, singlet, pyrrole H), 7.6 (4H, singlet, aromatic H); MS: (chemical ionization with methane) m/z 292 $(M+H)^+$. The specific activity of the labeled sample was determined to be 85 Ci/mmol (291 mCi/mg) by scintillation counting and calculation of the sample weight from absorption measurements using uv spectroscopy. The material co-chromatographed with an authentic sample of zomepirac in the following tlc systems: silica gel GF (Analtech, Inc.), chloroform/methanol/concentrated ammonium hydroxide (70:29:1, v/v, $R_f$ 0.37) and chloroform/glacial acetic acid (95:5, v/v, $R_f$ 0.67). Radiochemical purity was determined to be greater than 98% by tlc-radioscan in the above systems. No exchangeable tritium was found to be present after refluxing a portion of the sample for one hour in a solution of methanol containing sodium hydroxide. Distillation and scintillation counting of the distillate showed that the sample was free of labile tritium. The sample was stored at a radioactive concentration of 4.5 mCi/ml in 90% aqueous ethanol at -20°C and under a nitrogen atmosphere. Tlc-radioscans in the above systems showed the material to have a radiochemical purity of 95 - 96% after one year under the above storage conditions.

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