THE SYNTHESIS OF MULTIPLE DEUTERATED N-n-PROPYL-NORAPOMORPHINE N-(d_7) AND DERIVATIVES.

Yigong Gao*, Thomas M. Trainor§, Paul Vouros§, John L. Neumeyer*,
Section of Medicinal Chemistry, College of Pharmacy and Allied Health Professions*, Department of Chemistry§, Northeastern University, Boston, MA 02115

SUMMARY

NPA has been labelled using n-propyl iodide(d_7) through alkylation of norcodeine followed by a multistep route which also affords the related deuterated analogs N-n-propylnorapocodeine(d_7), the prodrug 10,11-methylenedioxy-NPA(d_7) and 10,11-dimethoxy-NPA(d_7).

Key Words: NPA, MDO-NPA, deuterium labelling, dopaminergic activity, apomorphine analogs.

INTRODUCTION

R(-)-N-n-propylnorapomorphine (NPA, 5a) has been thoroughly investigated due to its potent dopaminergic activity[1] (Figure 1). Consequently, the potential of the methylenedioxy derivative of NPA (MDO-NPA, 7a) as a prodrug in treating Parkinson's disease and related neurological disorders is under investigation. Additionally, the O-methylated analogs N-n-propylnorapocodeine (4a) and the corresponding 10,11-dimethoxy-N-n-propylnoraporphine (6a) are of interest in the study of potential metabolites of NPA[2]. Therefore, stable (nonradioactive) isotopes such as deuterium could be used to label these potential drugs to obtain analogs which would be useful for metabolic and pharmacokinetic studies and as true internal standards for GC-MS assays.

0362-4803/88/030293-07$05.00

Received February 25, 1987

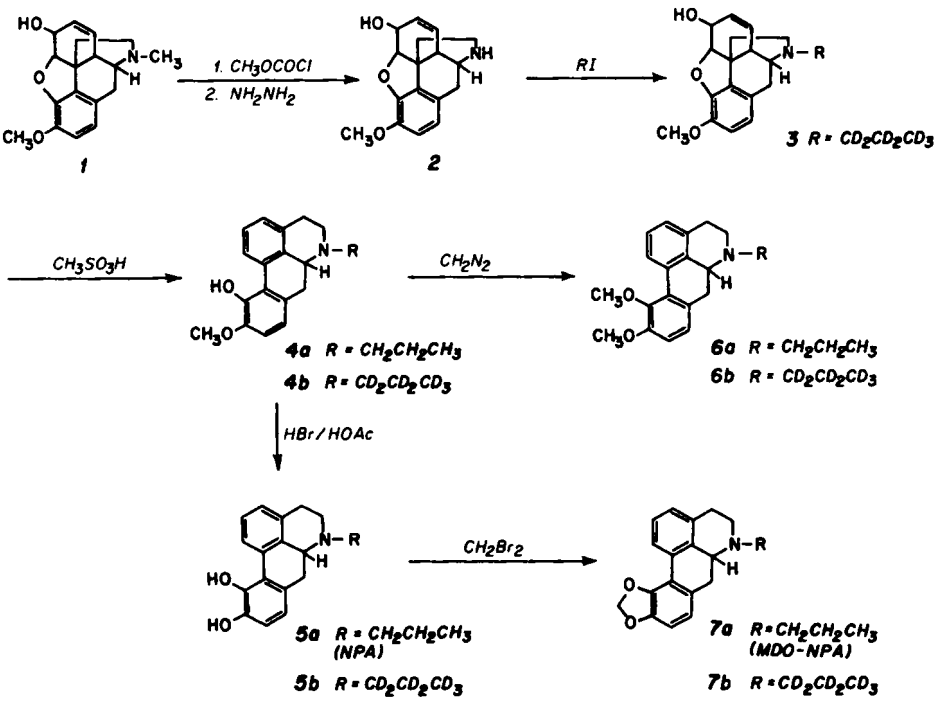

Figure 1.

Published studies on deuterium labelled apomorphine have dealt with deuteration at multiple sites along the aromatic ring structure[3,4]. However, these deuterated analogs were found to be unsuitable for use in stable isotope dilution mass spectrometry studies since hydrogen-deuterium exchange was found to occur quite readily[4,5]. For use as internal standards in mass spectrometry, the stable isotope analogs must provide for a mass increase of at least 3 amu to ensure no interferences between the ion clusters produced from the undeuterated and deuterated compounds. Retention of the heavy isotopes with at least one of the principal ions in the spectrum is also required. Moreover, scrambling or isotopic exchange must not occur during sample preparation steps (extractions, derivatizations) prior to mass spectrometric analysis. By incorporation of the N-alkyl moiety $-C_3D_7$ in N-n-propylnorapomorphine, and also, in the correspondings O-methyl, O,O'-dimethyl and 10,11-methylenedioxy derivatives, chemically stable and analytically useful isotope analogs have been prepared. In preliminary research, we have obtained a deuterium labelled

analog of apomorphine which was labelled in the 6a, 7 position of the aporphine ring[6]. This paper reports the development of a synthetic route to apomorphine analogs, which allows for the incorporation of up to seven deuterium atoms in the relatively stable N-alkyl side chain.

METHOD

The route which was envisaged for the synthesis of d_7-R(-)-apomorphine derivatives incorporated a conventional sequence which was based on the N-demethylation of codeine(1) using methylchloroformate to readily produce the carbamate intermediate. This was treated with hydrazine without purification to yield the corresponding norcodeine. The d_7 labelled products were prepared starting with the reaction of n-propyl iodide-d_7 and norcodeine in ethanol with Na_2CO_3 to yield (3). Rearrangement to N-n-propylnorapocodeine-d_7(4b) with methanesulfonic acid was carried out by previously described procedures[7]. Subsequent conversion to R(-)-NPA-d_7(5b) with HBr followed by methylenation of (5b) gave R(-)-MDO-NPA-d_7 (7b) as expected. Methylation of (4b) with CH_2N_2 provided 10,11-dimethoxy-N-n-propylnoraporphine-d_7 (6b) in good yield.

MASS SPECTOMETRY

All intermediates and final products were analyzed by electron impact ionization mass spectrometry via direct insertion probe introduction using a Finnigan 4021 GC/MS. Representative EI-MS spectra are included here for the MDO-NPA d_0 and d_7 pair, (Figure 2). Incorporation of the N-substituted $-C_3D_7$ group is confirmed by the presence of the molecular ion $M^{+\cdot}$ at m/z 314 for the d_7-MDO-NPA. Note also in the spectrum the lack of signal at m/z 307, the corresponding $M^{+\cdot}$ for the d_0-MDO-NPA compound. Examination of the mass spectra obtained for compounds(4b)-(7b) confirmed the presence of the desired labelled N-alkyl side chains (C_3D_7). Moreover, none of the labelled analogs revealed any evidence of H-D exchange under the synthetic

conditions employed. This feature, in conjunction with the availability of highly enriched n-propyl iodide-d_7 starting materials, has permitted the synthesis of materials of high isotopic purity (>98% d_7-) with no detectable quantities of the corresponding d_0 species. The d_7-NPA derivative is now being utilized in these laborotories as an internal standard for the trace level determination of NPA in rat serum and brain by gas chromatography-negative ion chemical ionization mass spectrometry[8].

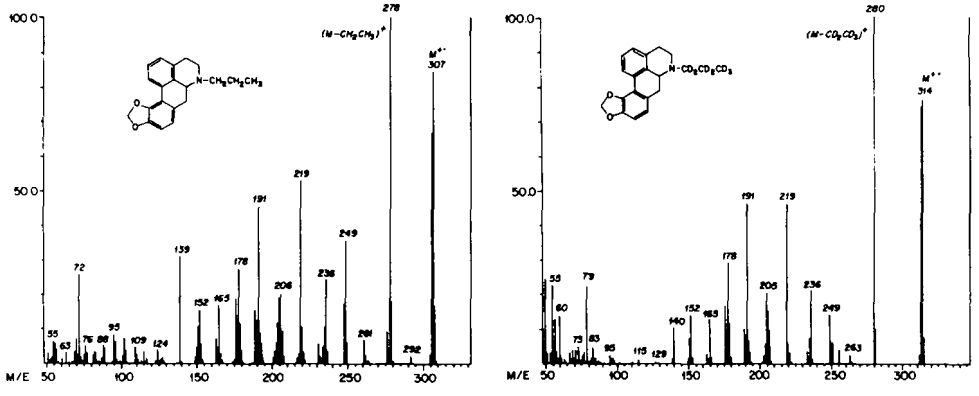

Figure 2.

EXPERIMENTAL PROCEDURES

All chemicals were used as received from the manufacturer. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-NMR spectra were obtained on Varian T-60 spectrometer using TMS as a reference.

Norcodeine (2).

A mixture of codeine (14g, 0.047mol), methyl chloroformate (86.31g, 0.91mol), and $NaHCO_3$ (63g, 0.75mol) in dried $CHCl_3$ (500ml) was stirred and refluxed 20 h. The reaction mixture was then filtered and the inorganic solids washed with fresh $CHCl_3$. The combined filtrate and washings were dried ($MgSO_4$) and evaporated to yield a white foam, which was dissolved in a mixture of anhydrous hydrazine(90ml) and MeOH(70ml), and the resulting solution allowed to reflux for 90 h. The mixture was cooled, diluted with H_2O(150ml), and extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and evaporated

to give crude solid product. Crystallization from acetone yielded 9.4g (70.4%) of (2) as white crystals, mp 185-186°C (lit[9]. 183-185°C).

N-n-propylnorcodeine-d_7 (3).

A mixture of 6.5g (0.0228mol) of norcodeine, 4.3g (0.0243mol) of n-propyl iodide-d_7, 4g (0.0289mol) of anhydrous potassium carbonate and 50ml of absolute ethanol was stirred under reflux for 22 h. This was followed by additon of 200ml of water, the solution was extracted with $CHCl_3$ and extracts dried over $MgSO_4$. Evaporation to dryness gave 7.6g (99.7%) of (3) as a clear oil, which gave only one spot on TLC (Silica with 10:1 $CHCl_3$/MeOH) and was used without further purification in the next step.

N-n-propylnorapocodeine hydrochloride-d_7 (4b).

To 1.4g(0.00419mol) of (3) in 20ml methanesulfonic acid was stirred under nitrogen at 90-95°C for 1 h. The solution was cooled and diluted with 30ml of water, then neutralized with concentrated ammonium hydroxide to pH 11 with stirring and cooling. The solution was extracted with $CHCl_3$ and the $CHCl_3$ extracts was shaken with successive portions of a sodium carbonate solution until all the low Rf material seen on TLC plate disappeared. After drying over $MgSO_4$ the hydrochloride was formed quantitatively by addition of ethereal hydrogen chloride solution to a $CHCl_3$ solution of the base. There was obtained 0.6g (41%) white solid of (4b). mp 168-170°C. Mass spectra: m/z 315(M^+). ^{1}H-NMR (CD_3OD, TMS) δ 8.42 [d, 1H, Ar-H #1], 7.37 [t, 1H, Ar-H #2], 7.18 [d, 1H, Ar-H #3], 6.87 [q, 2H, Ar-H_2 #'s 8,9], 4.89 [s, 1H, ArOH], 4.40 [m, 1H, CH], 3.90 [s, 3H, OCH_3], 2.81-3.52 [m, 6H, $(CH_2)_3$].

10,11-Dimethoxy-N-n-propylnoraporphine hydrochloride-d_7 (6b).

Methylation of (4b) was carried out with excess of diazomethane, which was made from Diazald (Aldrich), to afford a quantitative yield of free base of (6b) as an oil. Convertion to the HCl salt gave a white solid of (6b). mp 161-162°C. Mass spectra: m/z 331(M^+). ^{1}H-NMR (CD_3OD, TMS) δ 8.29 [d, 1H, Ar-H #1], 7.41 [t, 1H, Ar-H #2], 7.25 [d, 1H, Ar-H #3], 7.16 [d, 1H, Ar-H #8], 7.01 [d, 1H, Ar-H #9], 4.42 [m, 1H, CH], 3.90 [s, 3H, OCH_3], 3.67 [s, 3H, OCH_3], 2.81-3.52 [m, 6H, $(CH_2)_3$].

N-n-propylnorapomorphine hydrobromide-d_7 (5b).

A mixture of 1.9g (0.00538mol) of N-n-propylnorapocodeine hydrochloride-d_7 in 20ml of HBr(48%,w/v) and 20ml of glacial acetic acid was heated at 130-140°C under nitrogen for 4 h. and evaporated in vacuum. The residue was taken up with a minimal amount of absolute MeOH, and the solution was added dropwise to 400ml of ethyl ether to afford a precipitate. Filtration of the mixture yielded 1.97g (95.6%) of white solid of (5b). It sintered at 260°C and decomposed at 278-279°C. Mass spectra: m/z 302(M^+). ^{1}H-NMR (CD_3OD, TMS) δ 8.01 [d, 1H, Ar-H #1], 7.31 [t, 1H, Ar-H #2], 7.07 [d, 1H, Ar-H #3], 6.77 [d, 1H, Ar-H #8], 6.63 [d, 1H, Ar-H #9], 4.55 [m, 1H, CH], 2.79-4.13 [m, 6H, $(CH_2)_3$].

10,11-Methylenedioxy-N-n-propylnoraporphine hydrochloride-d_7 (7b).

To a mixture of 200mg (0.522mmol) of (5b) and 90mg of NaOH (2.25mmol) in 4ml of DMSO, a solution of 160mg (0.919mmol) of dibromomethane in 2ml of DMSO was added slowly over a period of 20 min. After the addition was completed, the reaction mixture was stirred at 80°C for a further 4 h. After cooling, water was added. The mixture was extracted with ethylacetate. The combined extracts were dried over $MgSO_4$ and evaporated to give an oil which was purified by flash chromatography. After converting to the HCl salt, 95mg (52%) of (7b) was obtained. mp 260-262°C (dec). Mass spectra: m/z 314(M^+). ^{1}H-NMR (CD_3OD, TMS) δ 8.07 [d, 1H, Ar-H #1], 7.41 [t, 1H, Ar-H #2], 7.22 [d, 1H, Ar-H #3], 6.88 [d, 1H, Ar-H #8], 6.79 [d, 1H, Ar-H #9], 6.17 [s, 1H, OCHO], 6.02 [s, 1H, OCHO], 4.44 [m, 1H, CH], 2.95-3.58 [m, 6H, $(CH_2)_3$].

ACKNOWLEDGMENT

We wish to acknowledge the support provided by NIH Grant NS-15439(JLN) and Research Biochemicals Inc. We also thanks MSD isotopes, Merck Frosst Canada Inc. for providing n-propyl iodide-d_7.

REFERENCES

1. Neumeyer J.L., Lal S. and Baldessarini R.J. in Apomorphine and other Dopaminomimetics, Vol 1 -Basic Pharmacology, Gessa G.L. and Corsini(eds) Raven Press, N.Y. 1981 pp1-17.

2. Neumeyer J.L., Abdel-Maksoud H.M., Trainor T.M., Vouros P. and Davis P.J. -Biomed. and Environ. Mass. Spectr. 13:223(1986)

3. Ginos J.Z., Lomonte A., Cotzias G.C., Bose A.K. and Bramsilla R.J. -J. Am. Chem. Soc. 95:2991(1973)

4. Soine W.H., Hudson J.E., Shoulders B.A. and Smith R.V. -J. Pharm. Sci. 9:1040(1980)

5. Soine W.H., Salgo P. and Smith R.V. -J. Labelled Cmpd. and Radiopharm. 16:597(1979)

6. Gottlieb R. and Neumeyer J.L. -J. Am. Chem. Soc. 98:7108(1976)

7. Granchelli F.E., Filer C.N., Soloway A.H.and Neumeyer J.L. -J. Org. Chem. 45:2275(1980)

8. Trainor T.M., Vouros P., Neumeyer J.L., Abdel-Maksoud H.M., Lampen P., Baldessarini R.J. and Kula N., in preparation.

9. Rice K.C. -J. Org. Chem. 40:1850(1975)