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Synthesis of *N*-[Methyl-^{11}C]Hydromorphone by Using Multivariate Strategies for Optimization of Radiochemical Yields

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The synthesis of *N*-[methyl-^{11}C]hydromorphone has been performed by using [^{11}C]methyl iodide and desmethyl hydromorphone in a mixture of dimethylsulphoxide and dimethylformamide as solvent. Optimization of the radiochemical yield by varying the reaction conditions was performed by using multivariate strategies [Box *et al.* Statistics for Experimenters (Wiley, New York, 1978);(1) Dean and Heald *Science* **189,** 805 (1975);(2) Carlsson *et al. Acta Chem. Scand.* **B7,** 9 (1983);(3) Spendley *et al. Technometrics* **4,** 441 (1962)(4)], such as simplex(4) and the response surface method RSREG in SAS (Statistical Analytical System) [SAS-version 5; available from SAS Insitute Inc., Box 8000, Cary, NC 27511-8000, U.S.A.(5)]. The labelled hydromorphone was obtained in 72% radiochemical yield in the alkylation reaction with [^{11}C]-methyl iodide, counted from the end of the [^{11}C]methyl iodide synthesis. *N*-[Methyl-^{11}C]hydromorphone was obtained as a ready injectable pharmaceutical solution with a total synthesis time of 40 min and in a 10% total radiochemical yield, with a radiochemical purity >99.5%, according to HPLC analysis.

Introduction

Such alkaloids as morphine, heroin, codeine, nicotine and bromocryptine have been prepared by *N*-alkylation of the corresponding desmethyl compound with [^{11}C]methyl iodide in such solvents as dimethylformamide (DMF) or acetonitrile in generally good radiochemical yields and with reaction times in the order of 5–10 min.(6)

Hydromorphone is an opiate receptor ligand of special interest. Ternes *et al.*(7) discovered that two species of macaque monkeys, cynomolgus and rhesus, showed differences in tolerance and physical dependence when treated with hydromorphone. By using PET (positron emission tomography), the distribution and kinetics of hydromorphone in brain of these species will be studied.

Difficulties were experienced in performing the *N*-alkylation reaction. The main problems were the low solubility of desmethyl hydromorphone in the solvents commonly used (ethanol, DMF, acetonitrile) in this type of reaction(6) and the large amount of side-products formed. To increase the radiochemical yield of labelled hydromorphone, two different optimization methods, simplex and the response surface method RSREG in SAS, were used. In these methods all the important variables are varied in the same set of experiments and the yield is determined. Factorial experiments were performed to sort out the important variables and to ascertain whether the variables were correlated or not. The important variables were found to be reaction temperature, solvent composition and concentration of desmethyl hydromorphone.

Scheme 1

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Experimental

General

Carbon-11 was produced in the tandem Van de Graaff accelerator at the University of Uppsala by the $^{14}N(p, \alpha)^{11}C$ reaction on a nitrogen gas target. The ^{11}C, obtained as carbon dioxide, was trapped in a 4-Å molecular sieve and transported to the chemistry laboratory. The carbon dioxide was released by heating the molecular sieves in a stream of nitrogen gas and [^{11}C]methyl iodide was synthesized using a remote-controlled synthetic system.(8) The [^{11}C]methyl iodide was trapped directly in a reaction vessel containing the desmethyl hydromorphone.

Analytical LC was peformed on Hewlett–Packard 1090 with a variable wavelength detector at λ = 284 nm, in series with a radiodetector. The analytical LC column was a 250 × 4.6 mm Alltech C-18, 10 μm with 0.05 M ammonium formate buffer, pH 3.5, and methanol was used as eluent. Semipreparative LC was carried out on a Waters system equipped with u.v. detector M-441 and a GM detector. A 250 × 10 mm Nucleosil C-18 (30 μm) column was used with 10% ethanol in 0.1 M ammonium formate, pH 3.5, as eluent. Large scale preparative LC was performed on a Waters PrepLC/System 500, using a C-18 column (PrepPAK-500/C-18) and a solution of 7% methanol in 0.1 M ammonium formate buffer, pH 3.5, as eluent. NMR (^{13}C and ^{1}H) spectra were recorded on JEOL FX 100 and JEOL FX 60. Mass spectra were run on an LKB 2091 mass spectrometer at 70 eV and on a Finnigan 4021 at 70 eV. Infrared spectra were run on a Perkin–Elmer 177 Grating Infrared Spectrophotometer.

Hydromorphone

In a 100-mL reaction flask equipped with a reflux condenser, 3.0 g (9.32 mmol) of morphine hydrochloride was dissolved in 30 mL of ethanol and 3 mL of 2 M hydrochloric acid; 0.16 g of palladium black was then added and the mixture was refluxed under nitrogen for 2 h. The catalyst was filtered off and the solvent removed in vacuum, 2.82 g (8.76 mmol) of crude product being obtained. The solid product was dissolved in 2 M hydrochloric acid and the pH adjusted to 8.67 with NaOH(aq). The precipitate was extracted into chloroform/isopropanol (3/1), dried with sodium sulphate and evaporated to give 2.10 g (6.52 mmol) of free base of the crude product.

In a saturated solution of sodium bisulphite,(9) 2.10 g (6.52 mmol) of the crude product was dissolved and stirred at 0°C for 1 h. The bisulphite addition product was filtered off to give 1.45 g (3.73 mmol). (IR (wave number, cm^{-1}): 1200 (S = 0), 1060 (S = 0), C = 0 at 1760 missing). The salt was treated with 2 M hydrochloric acid at 60°C for 1 h. The pH was adjusted to 8.67 with NaOH(aq) and the hydromorphone was extracted with 4 × 50 mL of chloroform/isopropanol (3/1). The combined organic layers were dried with sodium sulphate and the solvent removed in vacuum to give 0.64 g (2.24 mmol) of hydromorphone. The identity of hydromorphone was verified by ^{13}C-NMR(10) and MS.

^{13}C-NMR(100 MHz, (^{2}H)water): d = 20.2 (C-10), 24.5 (C-8), 32.6 (C-15), 39.5 (C-7), 40.9 (C-14), 45.2 (C-13), 47.7 (C-16), 61.0 (C-9), 90.4 (C-5), 118.4 (C-2), 121.3 (C-1), 122.6 (C-11), 125.5 (C-12), 138.6 (C-3), 143.5 (C-4), 212.1 (C-6). (C-17 is missing, perhaps included in C-14.)

MS[m/e(relative intensity/%)]: 286 (24.3, M′ + 1), 285 (100, M′+), 229 (31.4), 228 (33.0), 214 (19.0), 96 (24.7), 70 (18.3), 59 (20.4), 57 (18.5), 44 (26.5). (Only the major peaks are given.) Infrared (wave number, cm^{-1}): 3450 (OH), 1760 (C = 0).

Desmethyl hydromorphone

The synthesis of desmethyl hydromorphone was performed according to Ref. (11) with minor modifications.

^{13}C-NMR(10) and MS were used to verify the identity of the product. ^{13}C-NMR (100 MHz, (^{2}H)-DMSO): d = 24.1 (C-10), 24.8 (C-8), 31.5 (C-15), 37.0 (C-14), 39.2 (C-7), 42.0 (C-13) 45.2 (C-16), 51.0 (C-9), 89.7 (C-5), 117.8 (C-2), 119.8 (C-1), 121.4 (C-11), 125.8 (C-12), 140.0 (C-3), 144.0 (C-4), 207.6 (C-6).

MS[m/e (relative intensity/%)]: 272 (19.5, *M′* + 1), 271 (100, *M′*+), 228 (35.5) 214 (14.3), 200 (20.8), 171 (15.7), 161 (16.9), 115 (13.6), 82 (14.4), 68 (14.1). (Only the major peaks are given.)

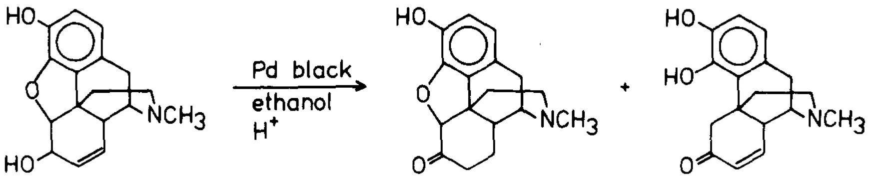
N-[Methyl-^{11}C]hydromorphone (Scheme 1)

In a 2-mL reaction vial, 0.4 mg of desmethyl hydromorphone was dissolved in 1 mL of a DMSO/DMF (53/47) solution. The [^{11}C]methyl iodide, produced as described earlier, was trapped in the vial at room temperature. After being kept at 107°C for 5 min, the reaction mixture was injected into a semipreparative HPLC column. Semipreparative LC was performed using the following conditions: flow 4 mL/min, isocratic 10% ethanol in 0.1 M ammonium formate buffer, pH 3.5. Conditions for analytical purposes were: flow 1–2 mL/min for 6 min, then 2 mL/min for 6 min. Eluents were A = methanol and B = ammonium formate buffer 0.05 M, pH 3.5, isocratic with 30% B for 6 min, then to 85% B during 2 min.

Experimental domain for optimization:
Concentration of desmethyl hydromorphone: 0.3–1.5 mg/mL
Reaction temperature: 70–140°C
Percent DMSO in DMF: 0–100.

Results and Discussion

The purification of the crude product obtained in the isomerization of morphine(12) (Scheme 2) presented some problems.(13) Weiss(14) found that a



Scheme 2

side-product, *O*-desmethylthebainone, was formed in the reaction and the amount of side-product was shown to be dependent on the type and quantity of catalyst.

The amount of hydromorphone in the crude product never exceeded 65% in our experiments. The remainder consisted of *O*-desmethylthebainone and a few percent of morphine, as determined by ^{13}C-NMR. Attempts to separate the compounds by extraction, recrystallization and precipitation failed. Purification using large-scale preparative HPLC was successful, giving the hydromorphone almost pure according to analytical HPLC. The drawback of this method was the large amounts of solvent that had to be removed. Accordingly, purification via the bisulphite addition product was our method of choice.

The reaction between a neutral nucleophile, such as the desmethyl compound, and an alkyl halide leads to a polar transition state. This formation is favoured by dipolar aprotic solvents, such as DMSO or DMF, so that the reaction time might be decreased and the temperature lowered, leading to fewer side-reactions. To suppress the alkylation of DMSO, a mixture of DMSO and DMF might be used.

In a general bimolecular reaction the following rate equation is relevant for the formation of the labelled product[15,16]

$$\frac{\mathrm{d}C^*}{\mathrm{d}t} = k_1 B A^* - \lambda C^*$$

where A^* is the concentration of labelled reagent, B the concentration of unlabelled reagent, C^* the concentration of labelled product and λ the decay constant for $^{11}\mathrm{C} = 0.0341454\ \mathrm{min}^{-1}$.

Since $A^* \ll B$, the kinetics is of pseudo first order. The specific activity of [^{11}C]methyl iodide is in the order of 10–100 mCi/μmol and the amount of radioactivity is in the order of 100 mCi, corresponding to 1 μmol of the labelled reagent. When the kinetics is of pseudo first order, the reaction rate can be accelerated by increasing B (in this case however, the poor solubility of desmethyl hydromorphone was a limiting factor). It has been shown[14] that, for rate constants in the order of $10^{-2}\lambda$–$10^{2}\lambda$, the yield of labelled product does not increase with reaction times longer than 10 min. In our study the [^{11}C]methyl iodide was totally converted within 5 min. The re-

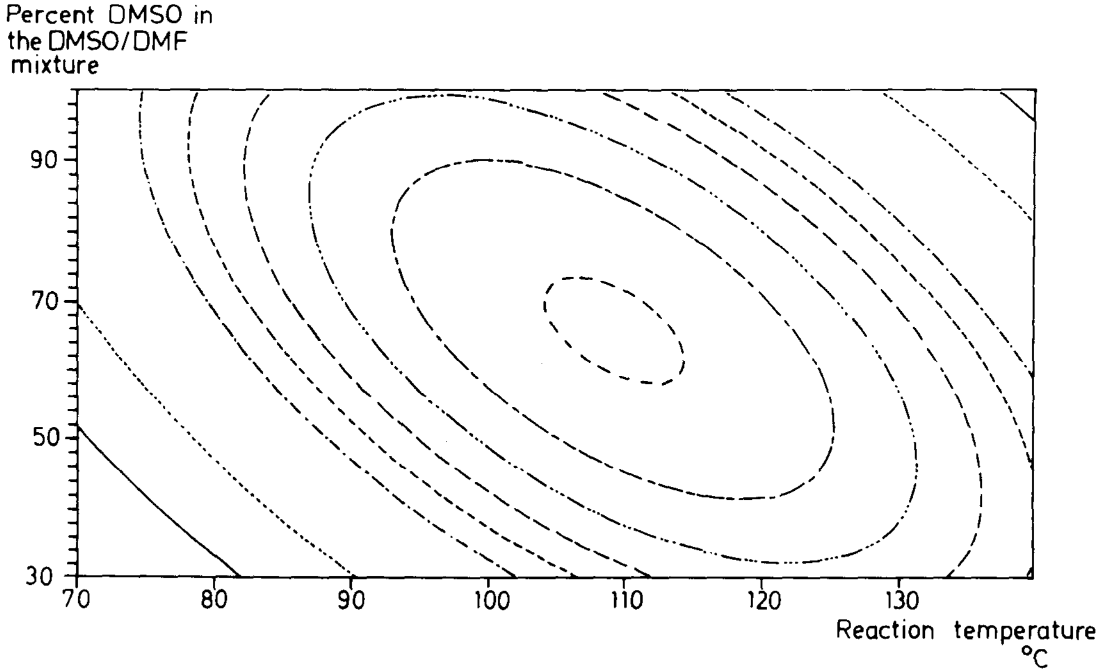


Fig. 1. Yield of *N*-[^{11}C-methyl]hydromorphone, —— 10; ···· 30; –·–·– 50; ---- 55; ——— 60; ·····–··– 65; –·–·– 70; –––– 75.

action time was therefore held constant in all experiments and not included in the optimization.

When performing factorial experiments, a model containing the effects, β_i, of each one of the three variables was used:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \times \beta_{12} x_1 x_2$$
$$\beta_{13} x_1 x_3 + \beta_{23} x_2 x_3 + \beta_{123} x_1 x_2 x_3 + \epsilon$$

Where x_1 was the concentration of desmethyl hydromorphone, x_2 the reaction temperature and x_3 the percent DMSO in the DMSO/DMF mixture. Experiments were performed where each variable was tested at two levels, e.g. 10% DMSO and 100% DMSO in the DMSO/DMF mixture, and the coefficients β_i were calculated.

The solvent composition, that is the percentage of DMSO in the DMSO/DMF mixture, was found to have the largest influence (= the largest β_i) on the yield of labelled hydromorphone. All variables were found to be correlated to one another, the largest correlation being between the percentage of DMSO in the DMSO/DMF mixture and the concentration of desmethyl hydromorphone. After the important variables were determined, the simplex procedure was followed. With n variables, $n + 1$ experiments have to be performed to create the first simplex. Based on the yields obtained, a new simplex was created, and a new experiment was performed with this new setting of the variables. This process was repeated until no further improvement in radiochemical yield was observed. The best yield, 75%, was obtained with a concentration of 0.4 mg/mL of desmethyl hydromorphone in 1 mL of a solution of DMSO/DMF (53/47) at 107°C.

When the approximate optimal setting of the variables was known, a response surface method was used. The response surface was described by a mathematical model containing quadratic terms to obtain the best description of a curved surface and showed the correlation between the variables, and the effect on yield when changing the setting of the variables. From this model we could see that the response surface had a large flat area where the optimum conditions were found, and the optimization was accordingly ended.

Our conclusion is that these multivariate strategies are a great help in the optimization of radiochemical yield. By using the simplex procedure the approximate setting of the variables for maximum yield can be found comparatively fast. The more sophisticated SAS procedure is useful when the shape of the response surface is of interest. When using this method only a smaller part of the response surface is investigated, this is to get the most accurate description, and therefore the approximate setting of the variables should be known. A limitation with both these methods, is the number of variables that can be included in the optimization, but by performing factorial experiments the most important variables can be sorted out.

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References

1. Box G. E. P., Hunter W. G. and Hunter J. S. *Statistics for Experimenters* (John Wiley, New York, 1978).
2. Dean K. K. and Heald K. J. *Science* **189,** 805 (1975).
3. Carlsson R., Nilsson Å. and Strömqvist M. *Acta Chem. Scand.* **B7,** 9 (1983).
4. Spendley W., Heat G. R. and Himsworth F. *Technometrics.* **4,** 441 (1962). The simplex program is available from Principal Data Components, 2505 Shepard Blvd, Colombia, MS 65201, U.S.A.
5. SAS—version 5; available from SAS Institute Inc., Box 8000, Cary, NC 27511-8000, U.S.A.
6. Långström B., Antoni G., Halldin C., Svärd H. and Bergson G. *Chem. Scrip.* **20,** 46 (1982).
7. Ternes J. W., Ehrman R. and O'Brien C. P. *Behav. Neurosci.* **99,** 3 (1985).
8. Långström B., Antoni G., Gullberg P., Halldin C., Någren K., Rimland A. and Svärd H. *Int. J. Appl. Radiat. Isot.* **37,** 1141 (1986); Långström B., Antoni G., Gullberg P., Halldin C., Malmborg P., Någren K., Rimland A. and Svärd H. *J. Nucl. Med.* (in press 1987).
9. Vogel A. I. *A Textbook of Practical Organic Chemistry* (Longmans, Green, London, 1962).
10. Assignment made by comparison with: Carroll F. I., Moreland C. G., Brine G. A. and Kepler J. A. *J. Org. Chem.* **41,** 996 (1976).
11. Brossi A., Atwell L., Jacobson A. E., Rozwadowska M. D. and Schmidhammer H. *Helv. Chim. Acta.* **65,** 2394 (1982).
12. Deutsches Reichspatentamt Nr 623821.
13. Gaal G. D. Acta Universitatis Debreceniensis. *Acta Phys. Chem.* **8,** 39 (1962).
14. Weiss U. and Weiner N. *J. Org. Chem.* **14,** 194 (1949).
15. Långström B., Obenius U., Sjöberg S. and Bergson G. *J. Radioanal. Chem.* **64,** 273 (1981).
16. Långström B. and Bergson G. *Radiochem. Radioanal. Lett.* **43,** 47 (1980).