# Synthesis of [2,3,4,5-$^{14}$C]-1-Vinyl-2-Pyrrolidinone

George A. Digenis[1*], J.S. McClanahan[1] and Pei-Lin Chen[1]

[1]Division of Medicinal Chemistry, College of Pharmacy

University of Kentucky, Lexington, KY 40536-0082

## SUMMARY

An efficient small scale synthesis of $^{14}$C labeled 1-vinyl-2-pyrrolidinone (NVP) is described. The cyclization of commercially available [1,2,3,4-$^{14}$C]-γ-aminobutyric acid (GABA) gives [2,3,4,5-$^{14}$C]-2-pyrrolidinone which is vinylized with vinyl acetate via a sodium tetrachloropalladate catalyst to give good yields of [2,3,4,5-$^{14}$C]-1-vinyl-2-pyrrolidinone

Key Words: polyvinylpyrrolidinone (PVP), 1-vinyl-2-pyrrolidinone (NVP), [$^{14}$C]-1-vinyl-2-pyrrolidinone, [$^{14}$C]-γ-aminobutyric acid, preparation.

## INTRODUCTION

1-vinyl-2-pyrrolidinone (NVP) (3) is a chemical intermediate from which polyvinylpyrrolidinone (PVP) is synthesized. PVP is widely employed in pharmaceutical and medicinal applications as well as in cosmetics, beer and foodstuffs due to its film-forming and adhesive properties, its colloidal and dispersing abilities and its capacity to form complexes with certain chemical compounds (e.g. polyacids, phenols and some tannins)(1).

The PVP preparations synthesized and employed in the above applications contain a small amount (0.2% or less) of NVP as an impurity(2). While the general population is not directly exposed to NVP as such, NVP still exhibits itself through its

*To whom correspondence should be addressed

0362–4803/93/010011–07$08.50

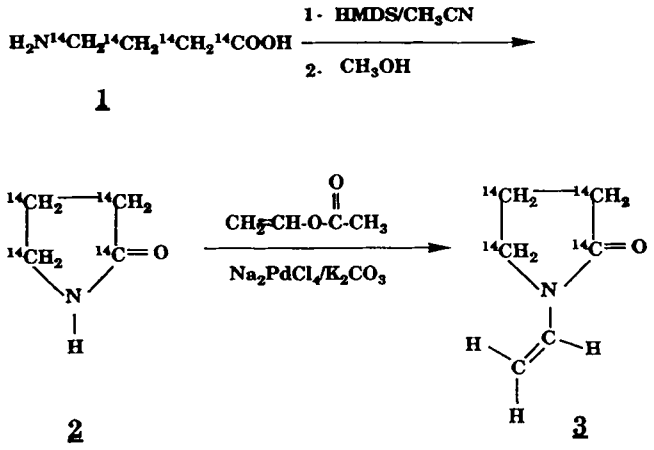
Received 29 May, 1992
Revised 30 July, 1992

broad based presence in PVP. The in vivo disposition and metabolism of NVP have been little described in the literature(3). In consideration of the widespread usage of PVP in the pharmaceutical and medicinal, food and beverage industries, studies on the in vivo disposition of NVP have been undertaken in this laboratory. The synthesis of [2,3,4,5-$^{14}$C]-1-vinyl-2-pyrrolidinone is described here.

## RESULTS AND DISCUSSION

Pellegata reported a method for the syntheses of lactams from their corresponding amino acids or hydrochloride salts(4). A novel synthetic procedure for the preparation of NVP from γ-aminobutyric acid (GABA) (1) has been developed which is adaptable to a very small scale. The method involves the vinylation of 2-pyrrolidinone (2) with vinyl acetate (Scheme1). [2,3,4,5-$^{14}$C]-2-Pyrrolidinone (2) was prepared by the cyclization of GABA (1) hydrochloride. According to the method of Pellegata(4), solvent (acetonitrile) had to be consecutively added to the reaction mixture in 1 mL increments at intervals of 2 hours due to the volatility of the acetonitrile. Therefore, some of the hexamethyldisilazane (HMDS) and the [2,3,4,5-$^{14}$C]-2-pyrrolidinone(2) evaporated during the reaction resulting in about a 25% loss of radioactivity. Thus, the method was modified to avoid this loss. The excess of HMDS, which was used as a solvent after the evaporation of the acetonitrile, was not added until the GABA (1) hydrochloride had dissolved in the acetonitrile. Due to this modification, the desired results were obtained (experimental section).

Based on the method of Bayer et al.(5) for the vinylation of lactams and imides, McClanahan made modifications for the preparations of NVP, [3,4-$^{3}$H]-NVP and [4-$^{3}$H]-NVP(6). The




1 2 3

**Scheme 1**

chemical yields were, 17%, 19.2% and 13.3% respectively(6). The procedure was repeated and preparative thin-layer chromatography was used to isolate the NVP. It was found that the volatility of NVP was responsible for the low yields of McClanahan's procedure. Evaporation of the solvent resulted in a 20-40% loss of radioactivity. The loss depended on the elution system. When the solution, consisting of approximately 2 mg NVP in 10 mL of methanol or in 25 mL of acetone, was evaporated at 0°C, the loss was 35% and 18% respectively. In McClanahan's procedure the reaction mixture was refluxed for 71 hours under an argon atmosphere and most of the vinyl acetate (solvent) escaped with the argon, which also led to the loss of NVP. In view of these facts, the reaction was run at 50-60°C with no reflux and evaporation of the solvent (acetone) was carried out at 0°C. Purification by TLC produced 3 (93.5% radiochemical purity, 73.7% chemical yield, 73.0% radiochemical yield).

## MATERIALS AND METHODS

Reagents:

[1,2,3,4-$^{14}$C]-γ-aminobutyric acid was purchased from DuPont de Nemours and Company Inc. (Wilmington, DE). γ-Aminobutyric

acid, hexamethyldisilizane, vinyl acetate and sodium tetrachloropalladate were obtained from Aldrich Chemical Company (Milwaukee, WI). The molecular sieve (4 Å) was obtained from J.T. Baker Chemical Company (Phillipsburg, NJ).

Instrumentation:

NMR spectra were taken in $CDCl_3$ using tetramethylsilane as an internal standard and recorded on a Varian VXR 300 MHz spectrometer. Radioactive samples were counted in a Packard Model 337S Tri-carb liquid scintillation spectrometer (Packard, Downers Grove, IL) using Fisher Scintiverse II liquid scintillation cocktail (Fisher, Pittsburg, PA).

High Performance Liquid Chromatography:

Analyses of samples for identification and radiochemical purity were performed using a reversed-phase HPLC system consisting of an Altex Model 110A solvent metering pump (Altex Scientific, Berkeley, CA), and a Spectroflow 773 UV detector (Kratos Analytical Instruments, NJ). Samples were introduced via a Rheodyne loop injector (Rheodyne, Cotati, CA) equipped with a 50 µl loop onto an µBondapak C-18 Column, 30 cm x 4.0 mm ID (Waters Associates, Milford, MA)(7). The effluent was split by a Radiomatic Model ES streamsplitter (Radiomatic Instruments and Chemicals Co., Tampa, FL) after it has passed through the UV detector, with 50% going to a Radiomatic Model HP Flo-One radioactive flow detector and 50% to waste. The UV output was recorded on a Linear Model 500 strip chart recorder (Linear Instruments Corp., Reno, NV). The programmable radioactive flow detector mixed scintillation cocktail (Scintiverse L.C., Fisher Scientific, Pittsburgh, PA.) with effluent in a ratio of 3:1, by volume(6). The radioactivity output was recorded simultaneously on the second channel of the recorder.

Methods:

γ-Aminobutyric Acid Hydrochloride.

γ-Aminobutyric acid (1) (10 mg, 0.097 mmol) was dissolved in 0.01 mL of 12N HCl (0.12 mmol) and 1.5 mL of $H_2O$. Benzene (20mL) was added to the solution and the mixture refluxed, to remove the water and HCl by azeotroping, until no water was collected. The mixture was then evaporated to dryness and 12 mg of a white hygroscopic solid was obtained (89.5% yield, mp 125-126°C, lit. mp 135-136°C)(8).

[2,3,4,5-$^{14}$C]-2-Pyrrolidinone (2)

Conversion of 1 hydrochloride to 2 was adapted from the method of Pellegata(4). To an aqueous solution (2.5 mL, 0.01N HCl) of [1,2,3,4-$^{14}$C]-GABA (250 µCi, 233 mCi/mmol) was added unlabeled GABA hydrochloride (15.3 mg, 0.11 mmol), resulting in a specific activity of 2.26 mCi/mmol. The solution was freeze dried and then 1.5 mL of acetonitrile added. The suspension was refluxed with stirring. After the GABA HCl had dissolved, hexamethyldisilazane (HMDS,1.5 mL, 7.1 mmol) was added to the flask. The mixture was stirred for 24 hr at 80°C (bath temperature) under a nitrogen atmosphere. The yellowish solution was then cooled to room temperature and 5 mL of methanol was added. The volatile components were evaporated under reduced pressure at 0°C. Chloroform (4 mL) was then added to the oil residue and the resulting suspension filtered. Next, the filter cake was washed with small amounts of chloroform. The rinses were combined, transferred to a 10 mL volumetric flask and then chloroform added to the 10 mL mark. This solution was used for the determination of radioactivity and mass (UV). Finally, the chloroform was evaporated under reduced pressure at 0°C to give 2 (5.9 mg, 158.9 µCi, 2.13 mCi/mmol, 63.3% chemical yield, 63.6% radiochemical yield). Radiochemical purity of the product,

determined by HPLC using methanol/water (10:90, v/v) as the mobile phase with a flow rate of 1.0 mL/min and UV detection at 210 nm, was 94.0%. The retention time (5.4 min) of synthesized 2 corresponded to that of standard unlabeled and ([2-$^{14}$C]) labeled 2-pyrrolidinone. The specific activity and mass of the sample were determined using the same HPLC conditions.

[2,3,4,5-$^{14}$C]-1-Vinyl-2-Pyrrolidinone (3)

The procedure used was an adaptation of the method of Bayer et al.(5) for the vinylation of lactams and imides.

Into a 10 mL round bottom flask containing 2 (5.8 mg, 68.3 mmol, 150 µCi, 2.13 mCi/mmol, 94% radiochemical purity) and 2 mL vinylacetate were added sodium tetrachloropalladate (15.9 mg, 59.1 mmol), potassium carbonate (17.4 mg, 105.3 mmol), and 4 Å molecular sieves (103.5 mg). The mixture was stirred and heated at 55-60°C (bath temperature) for 24 hr under an argon atmosphere. When cooled, the mixture was filtered and the cake washed with small amounts of methylene chloride. The resulting solution was cooled to 0°C and then concentrated to about 0.5 mL under reduced pressure. Compound 3 was isolated using a preparative TLC (Whatman silica gel plate, 250 µm, 20 x 20 cm, developing system: ethyl acetate/petroleum ether (1:1.5, v/v), extracted with 1.5 mL acetone, and then measured by UV (230 nm). Finally, the acetone was evaporated under reduced pressure at -5°C to give 3 (5.73 mg, 73.7% chemical yield, 110.0 µCi, 1.99 mCi/mmol, 73.0% radiochemical yield). Radiochemical purity of the product, determined by HPLC using methanol/water (20/80, v/v) as the mobile phase with a flow rate of 1.0 mL/min and UV detection at 230 nm, was 93.5%. The retention time (11.0 min) of the product corresponded to that of standard unlabeled and [2,3,4,5-$^{14}$C] labeled 1-vinyl-2-pyrrolidinone. The specific

activity and mass of the sample were determined using the same HPLC conditions(7). The NMR spectrum of 3 corresponded to that of unlabeled NVP.

## REFERENCES


1. Robinson B.V., Sullivan F.M., Borzelleca J.F., Schwartz, S.L. PVP. A critical review of the Kinetics and Toxicology of Polyvinylpyrrolidone (Povidone). Lewis Publishers, Chelsea, Mi, 1990.
2. United States Pharmacopeia, USP XXII (1990) United States Pharmacopeial Convention Inc., Rockville, MD 20852.
3. McClanahan J.S., Lin Y.C., Digenis G.A. Drug Chem. Toxicol., 7: 129 (1984).
4. Pellegata R., Pinza M. and Pifferi G. - Synthesis 8: 614 (1978).
5. Bayer E., and Geckeler K., Angew. Chem. Int. Ed. Engl. 18: 533 (1979).
6. McClanahan J.A., Ph.D. Dissertation, University of Kentucky, Lexington (1984).
7. Yamakita H., Page R.C., Digenis G.A. J. Liquid Chromat. 15: 83 (1992).
8. Windholez M. Ed., The Merk Index. 9th ed., Merck and Company. Inc., Rahway, New Jersey, p. 996 (1976).