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Synthesis of 3,3-Bis(3-fluorophenyl)-[2,3-$^3H_2$]-1-propanamine Hydrochloride ([$^3H_2$]-NPS 846·HCl): A Novel Ligand for the NMDA Receptor

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SUMMARY

3,3-Bis(3-fluorophenyl)-1-propanamine hydrochloride (NPS 846·HCl, **1a**) is representative of a new class of diphenylpropylamine NMDA receptor antagonists. The corresponding radiolabelled ligand was prepared by catalytic tritiation of its precursor olefin (**4**), which was synthesized in a three-step reaction sequence starting from 3,3'-difluorobenzophenone (**2**). Catalytic tritiation of **4** was performed in a two-component solvent system ([3:1] 1,4-dioxane/methanol). The percentage of isotope incorporation was found to be dependent on the nature of the reaction solvent. Experiments with deuterium gas indicate that higher radiochemical incorporation can be obtained by reduction in either neat 1,4-dioxane or methyl alcohol-*d*.

Key Words: [$^3H_2$]-NPS 846·HCl, NMDA receptor antagonists, catalytic tritiation

INTRODUCTION

Recently, we reported the discovery of a novel class of NMDA receptor antagonists, the diphenylpropanamines.[1-3] NPS 846 hydrochloride (**1a**) is representative of this class and shows potent *in vitro* NMDA receptor antagonist activity. It produces a significant neuroprotective effect at

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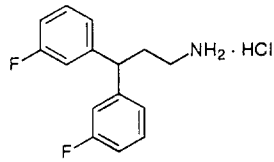
doses of 1 mg/kg (i.v.) in animal models of temporary focal cerebral ischemia presumably by providing protection against excitotoxic amino acid-induced neuronal degeneration.[4-6] A congener, NPS 1506·HCl, is currently undergoing human clinical evaluation.[1,7]

Glutamate is the major excitatory neurotransmitter in the mammalian CNS, where it acts on at least three subtypes of ionotropic receptors. These receptors have been classified pharmacologically as *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainate receptors, according to their preferred agonists.[8-9] Glutamate receptors have been implicated in the physiology and pathophysiology of various neurological functions and disorders such as ischemic stroke, epilepsy, pain, depression, and various neurodegenerative disorders such as Parkinson's disease.



NPS 846·HCl (**1a**)

Activation of glutamate receptors during and after an episode of focal or global ischemia appears to contribute significantly to the pathological outcome.[10] It has been postulated that the NMDA receptor subclass may play a key role in mediating neuronal damage, possibly due to its high permeability to calcium, a known mediator of cell death.[11-12] In animal models of focal ischemia, NMDA receptor antagonists provide more dramatic and consistent neuroprotection than any other class of compounds.[13]

In summary, we have prepared tritiated NPS 846·HCl (**1c**) for use experimentally as a radiochemical label for the investigation of this novel class of glutamate receptor ligand. We hope that this new tool can be used to further our understanding of the chemistry and pharmacology of this specific ligand-receptor interaction, as well as find uses in pharmacokinetic and drug metabolism studies.

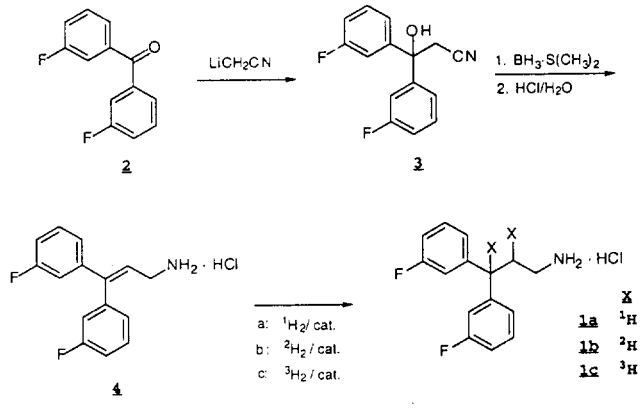
RESULTS AND DISCUSSION

Tritiated NPS 846·HCl (**1c**) was synthesized in a three-step reaction sequence starting from commercially available materials (see Reaction Scheme). 3,3'-Difluorobenzophenone (**2**) was condensed with the lithium anion of acetonitrile to provide the intermediate nitrile alcohol (**3**).

Reduction of the nitrile functionality of 3 was accomplished using borane-dimethyl sulfide complex. Work-up of this reaction with strong mineral acid afforded the dehydration product (4).

The olefin (4) was reduced with tritium gas over a catalytic amount of 10% palladium on charcoal in [3:1] 1,4-dioxane/methanol. Methanol was added in order to solubilize the olefin hydrochloride in the 1,4-dioxane prior to reduction. Following catalyst filtration, the excess tritium gas, as well as the exchangeable tritiums on the nitrogen atoms, were removed by several evaporations with ethanol under vacuum. The resulting crude radiolabelled product was purified by thin-layer chromatography (TLC) on silica gel to give the title compound (1c). The radiochemical purity was found to be 99.0% by analytical HPLC and 98.2% by TLC. The specific activity was determined (by mass spectral analysis) to be 39.2 Ci/mmol and the radiochemical incorporation was calculated to be 65%.

Reaction Scheme: Synthesis of Tritiated NPS 846



Subsequent experiments indicate that methanol, added to the reaction mixture in order to solubilize compound 4, might have been, at least in part, responsible for the loss of radiochemical incorporation into the product. Solvent exchange with tritium gas in alcoholic solvent systems has been reported in the literature.[14-16] In addition, the catalytic reduction step was performed using the hydrochloride salt (4), where the slight acidity of the reaction mixture, as well as the presence of labile $-NH_3^+$ protons, might possibly contribute to lowering the specific activity of the reduction product. We have since conducted experiments with deuterium gas in an effort to increase the percentage of label incorporation for use in the preparation of 1c with the highest possible specific activity. Toward this goal, we deuterated 4 in four different solvent systems under otherwise identical reaction conditions.

Table 1. Effect of Reduction Solvent on the Percentage of Isotope Incorporation into **1b**

	(%)			
solvent system	dihydrogenated product (*m/z* 247)	monodeuterated product (*m/z* 248)	dideuterated product (*m/z* 249)	total deuterium incorporation
MeOD	0	0	100	100
1,4-dioxane	0	11	89	95
[3:1] 1,4-dioxane/MeOH	5	27	68	82
MeOH	5	29	66	81

We subsequently found that **4** will dissolve into 1,4-dioxane at 40 °C, thereby eliminating the need for the addition of methanol. In agreement with the results of experiments reported in the literature,[14-16] we observed 95% total deuterium incorporation when 1,4-dioxane alone was used as the solvent (see Table 1). However, 11% monodeuteration was also observed under these conditions. Reductions performed in methyl alcohol-*d* (MeOD) provided 100% pure dideuterated product (**1b**). Lower total deuterium incorporation (81-82%) was found when either [3:1] 1,4-dioxane/methanol or methanol (MeOH) alone was used as the reduction solvent. The percentages of isotope incorporation were determined by mass spectrometry using extracted ion chromatograms, and the results are summarized in Table 1.

SUMMARY

[2,3-$^{3}H_2$]-NPS 846·HCl (**1c**) was prepared in high radiochemical purity with a specific activity of 39.2 Ci/mmol (65% tritium incorporation). The radiochemical label was incorporated into NPS 846·HCl by catalytic tritiation of alkene (**4**) over palladium on charcoal. The crude radiolabelled product was purified by preparative-TLC and the radiochemical purity was determined to be 99% by HPLC.

Subsequent studies using deuterium gas showed that complete deuterium incorporation can be obtained by running the catalytic reduction in methyl alcohol-*d*. A small amount of monodeuteration (11%) was observed when 1,4-dioxane was used as the solvent (see Table 1). The addition of a protic solvent (*i.e.*, methanol) increased the relative amounts of both the undeuterated product and the monodeuterated product. Thus, in accord with the literature[14-16], the total amount of deuterium incorporation was shown to be lower when using protic solvent systems.

EXPERIMENTAL SECTION

^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were acquired on a Varian Gemini NMR spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C); chemical shifts are reported as δ values (ppm) relative to Me_4Si. Coupling constants (*J*) are reported in hertz (Hz). Capillary gas chromatographic and low-resolution mass spectral data were obtained using a Hewlett-Packard (HP) 5890 Series II Gas Chromatograph coupled to an HP 5971 Series Mass Selective Detector [Ultra-2 Ultra Performance Capillary Column (crosslinked 5% PhMe silicone); column length, 25 m; column i.d., 0.20 mm; Helium flow rate, 60 mL/min; injector temp., 250 °C; temperature program, 20 °C/min from 125 to 325 °C for 10 min, then held constant at 325 °C for 6 min]. Thin-layer chromatography was performed using Analtech Uniplate™ 250-μM silica gel HF TLC plates. UV light in conjunction with ninhydrin and Dragendorff's spray reagents (Sigma Chemical Co.) were used for detecting compounds on the TLC plates. Melting points were determined in open capillary tubes on a Mel-Temp II apparatus and are uncorrected. Reagents used in reactions were purchased from the Aldrich Chemical Co. (Milwaukee, WI). Catalysts were purchased from the Fluka Chemical Corp. (Ronkonkoma, NY).

3,3-Bis(3-fluorophenyl)-3-hydroxypropionitrile (3)

A solution of acetonitrile (2.35 g, 57.3 mmol) in tetrahydrofuran (THF, 30 mL) was added dropwise over a period of 5 min to a cooled solution (-78 °C) of butyllithium (22.9 mL, 57.3 mmol, 2.5 M in hexane) in dry THF (100 mL). After stirring at -78 °C for 30 min a solution of 3,3'-difluorobenzophenone (10.0 g, 45.8 mmol) in THF (50 mL) was then added dropwise over a period of 20 min. The reaction mixture was stirred at -78 °C for 1 h and then quenched by the addition of satd. aq. NH_4Cl (100 mL). The mixture was allowed to warm to room temperature. The resulting layers were separated and the aqueous layer was extracted with Et_2O (2 x 50 mL). The combined organic layers were washed first with satd. aq. NaCl (2 x 20 mL) and then with H_2O (20 mL). The combined extracts were dried (anh. Na_2SO_4) and the solvent was evaporated under vacuum. Residual H_2O was azeotroped off with abs. EtOH (2 x 25 mL). The crude product was dissolved in hot $CHCl_3$ (50 mL); hexane (100 mL) was added, and the solution was slowly evaporated under vacuum until crystals appeared. The flask was then cooled in an ice bath. The crystals were collected, washed with ice-cold hexane, and dried to provide 10.7 g (90%) of product **3**: ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.95 (s, 1H, -OH), 3.23 (apparent s, 2H, -CH_2-), 6.95-7.38 (m, 8H, Ar-H); mp 99-100 °C; GC, t_R = 8.48 min; MS (EI), *m/z* 259 (M^+).

3,3-Bis(3-fluorophenyl)prop-2-en-1-amine hydrochloride (4)

A solution of 3 (10.5 g, 40.5 mmol) in dry THF (200 mL) was heated to boiling. $BH_3{\cdot}S(CH_3)_2$ (20 mL, 202 mmol, 10.1 M) was then added dropwise over a period of 2 min. The reaction solution was allowed to boil (no condenser) for 30 min. After most of the solvent had evaporated, the reaction mixture was cooled in an ice bath. The reaction was quenched by the careful addition of ice (10 g), H_2O (50 mL), followed by conc. HCl (100 mL). The reaction mixture was subsequently heated to boiling (no condenser) for an additional 30 min. The reaction mixture was cooled in an ice bath and was then made alkaline by the addition of 10*N* NaOH (110 mL) and the crude product was extracted with Et_2O (2 x 200 mL). The combined organic layers were washed first with 1*N* NaOH (50 mL), then with H_2O (50 mL), dried (anh. Na_2SO_4), and evaporated under vacuum. The residue was dissolved in Et_2O (100 mL) and the resulting solution was acidified by the addition of excess 1.0 M ethereal HCl (50 mL). The acidic solution was then evaporated under vacuum and the crude product was recrystallized twice from [1:10] 2-propanol/Et_2O (385 mL) to provide 7.37 g (65% yield) of the desired product as a white solid: ^{1}H NMR (300 MHz, DMSO, HCl salt), δ 3.46 (bm, 2H, -C$\underline{H}_2$-), 6.32 (t, J = 7.0 Hz, 1H, C=C$\underline{H}$), 7.00-7.52 (m, 8H, Ar-$\underline{H}$), 8.46 (bs, 3H, -N$\underline{H}_3^+$); ^{13}C NMR (75 MHz, DMSO, HCl salt) δ 38.2 (-$\underline{C}H_2$-NH_3^+), 114.0 (d, $J_{C\text{-}F}$ = 22.2 Hz, Ar-C2,2'), 115.2 (d, $J_{C\text{-}F}$ = 9.7, Aliph-CH), 115.5 (d, $J_{C\text{-}F}$ = 9.1, Aliph-CH), 116.6 (d, $J_{C\text{-}F}$ = 21.6, Ar-C4,4'), 126.0 (d, $J_{C\text{-}F}$ = 2, Ar-C6,6'), 131.0 (d, $J_{C\text{-}F}$ = 8.6, Ar-C5), 131.1 (d, $J_{C\text{-}F}$ = 8.0, Ar-C5'), 140.1 (d, $J_{C\text{-}F}$ = 8.0, Ar-C1), 142.7 (Aliph-Q), 143.2 (d, $J_{C\text{-}F}$ = 8.0, Ar-C1'), 162.6 (d, $J_{C\text{-}F}$ = 242, Ar-C3,3'); mp 199-200 °C (dec.); UV/Vis, ε = 8.0 x 10^3 L·mol^{-1}·cm^{-1} (264 nm, EtOH, 25 °C); GC, t_R = 7.96 min; MS (EI), *m/z* 245 (M^+).

3,3-Bis(3-fluorophenyl)-[2,3-$^3H_2$]-1-propanamine hydrochloride (1c)

A solution of the olefin, 4 (14 mg, 0.050 mmol), in [3:1] 1,4-dioxane/MeOH (2.0 mL) was reacted at room temperature with tritium gas (1 atm) over 10% Pd/C (7 mg) in a stainless steel apparatus. After 4 h, the catalyst was removed by filtration and excess tritium was removed by several evaporations under vacuum with EtOH. The resulting crude product was dissolved in EtOH and purified by preparative-TLC [silica gel plates, $CHCl_3$-MeOH-NH_4OH (80:20:1)]. The band corresponding to the product (visualized under UV light) was isolated and eluted from the plate with EtOH (30 mL). An equivalent amount of 0.1*N* HCl (0.1 mL) was added to give the title compound (1c) (2.9 mg, 20% yield). The radiochemical purity of the purified product was determined to be 99% by HPLC [Vydac Pro-Prep C-18 analytical column; 250 mm x 4.6 mm; 5 μM; 90 Å; 0.2% aq. trifluoroacetic acid (65:35) (TFA)/CH_3CN] and 98.2% by TLC [silica gel, (7:3:0.1)

$CHCl_3$/MeOH/NH_4OH]. The specific activity was determined to be 39.2 Ci/mmol by mass spectral analysis, which provided a calculated radiochemical incorporation of 65%. Physical data for the product (1a) obtained using hydrogen gas were: ^{1}H NMR (300 MHz, DMSO, HCl salt), δ 2.39 (m, *J* = 7.5 Hz, 2H, -CH-C$\underline{H}_2$-), 2.65 (apparent t, *J* = 7.8, 2H, -C$\underline{H}_2$-NH_3^+), 4.30 (t, *J* = 8.1, 1H, -C$\underline{H}$-), 7.0-7.4 (m, 8H, Ar-$\underline{H}$), 8.32 (bs, 3H, -N$\underline{H}_3^+$); ^{13}C NMR (75 MHz, DMSO, HCl salt) δ 32.0 (-$\underline{C}H_2$-NH_3^+), 37.5 (-CH$\underline{C}H_2CH_2$-), 46.6 (-$\underline{C}$H-), 113.7 (d, $J_{C\text{-}F}$ = 20.6 Hz, Ar-C2,2'), 114.6 (d, $J_{C\text{-}F}$ = 21.1, Ar-C4,4') 124.1 (d, $J_{C\text{-}F}$ = 2.9, Ar-C6,6'), 131.0 (d, $J_{C\text{-}F}$ = 8.0, Ar-C5,5'), 146.7 (d, $J_{C\text{-}F}$ = 6.9, Ar-C1,1'), 163.0 (d, $J_{C\text{-}F}$ = 244, Ar-C3,3'); mp 207.5-208.0 °C; UV/Vis ε = 1.9 x 10^3 L·mol^{-1}·cm^{-1} (264 nm, EtOH, 25 °C); GC, t_R = 7.94 min; MS (EI), *m/z* 247 (M^+).

3,3-Bis(3-fluorophenyl)-[2,3-$^2H_2$]-1-propanamine hydrochloride (1b)

Under an atmosphere of argon in 6-dram, oven-dried vials equipped with magnetic stirring bars and rubber septa, the alkene, 4 (50.0 mg, 17.8 mmol), was dissolved into each of the various reaction solvents [5 mL; (1) methyl alcohol-*d*, Aldrich Chem., 99.5 + atom % D; (2) 1,4-dioxane, Aldrich Chem., anhyd., 99.8%, < 0.005% H_2O; (3) [3:1] mixture of 1,4-dioxane-methanol; and (4) methanol, Aldrich Chem., anhyd., 99.8%, < 0.005% H_2O]. Each of the above solutions was then transferred, via syringe, to separate 6-dram vials each containing catalyst (20.0 mg, 10% palladium on activated charcoal, Fluka Chem.) suspended in the appropriate reaction solvent (15 mL), under an atmosphere of argon. Round, rubber balloons (helium quality, Latex Occidental, American Imports, San Antonio, TX) containing deuterium gas (approx. 3 L, Aldrich Chem., 99.98 atom % D) were attached to the septa via syringe needles. The reaction mixtures were purged with the deuterium gas for approximately 2 min and were then stirred under an atmosphere of deuterium gas at 25 °C.

After 6 h, each of the above reaction mixtures was prepared for analysis. The catalyst from each vial was removed by filtration (0.45 μM, PTFE syringe filters) and the various solvents were independently evaporated under vacuum. The crude products were then dissolved in EtOH (2 x 15 mL) and the solvents were evaporated under vacuum. These evaporation procedures were necessary prior to mass spectral analysis so that the residual deuterium associated with the amine nitrogens in the samples would exchange with hydrogens.

Aliquots of each sample were then analyzed by capillary gas chromatography/mass spectrometry (GC/MS). Isotope incorporation into the products was determined by analyzing the GC/MS data using extracted ion chromatograms. Observed mass/charge (*m/z*) ratios were: (1) 247, dihydrogenated product; (2) 248, monodeuterated product; (3) 249, dideuterated product; and (4) 250, for the M+1 peak of the dideuterated product.

The raw data generated by the mass spectrometer for various relevant ion peak areas were mathematically manipulated to remove "artificial" increases in the *m/z* 248 and 249 peak areas due to natural isotope abundances. The data were "corrected" by subtracting peak areas due to natural isotope abundance, i.e., "M+1" by: first, subtracting 18.6% of the area of the 247 peak from the 248 peak to provide a "corrected" 248 peak area; and second, by subtracting 18.6% of the "corrected" 248 peak area from the 249 peak to provide a "corrected" 249 peak area. The 18.6% natural isotope abundance increase in the M+1 peak was experimentally determined from the mass spectrum of NPS 846 (1a). The natural isotope abundance of NPS 846 was calculated to be 16.9%.[17]

Catalytic deuteration of compound 4 in methanol-*d* provided 100% deuterium incorporation in the double-bond reduction. 1,4-Dioxane provided the desired product with 95% deuterium incorporation. Experiments run in the protic mixtures provided 80-81% deuterium incorporation. The results from the above experiment are shown in Table 1.

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REFERENCES

1. Mueller, A.L.; VanWagenen, B.C.; DelMar, E.G.; Balandrin, M.F.; Moe, S.T.; and Artman, L.D.–Arylalkylamine compounds active at a novel site on receptor-operated calcium channels useful for the treatment of neurological disorders and diseases, and preparation of these compounds. *PCT Internatl. Appl. WO* 95/21,612 (August 17, 1995); *U.S. Patent Appl.* 14,813 (February 8, 1993), 139 pp.; *Chem. Abstr.* 123(23): P 306618t (1995).
2. Balandrin, M.F.; VanWagenen, B.C.; DelMar, E.G.; Artman, L.D.; and Mueller, A.L.–Discovery, design, and *in vitro* biological evaluation of NPS 846 and its congeners: Novel NMDA receptor antagonists. *37th Annual Meeting of the American Society of Pharmacognosy*, O19, University of California, Santa Cruz, California, July 27-31, 1996.
3. VanWagenen, B.C.; Balandrin, M.F.; DelMar, E.G.; Artman, L.D.; and Mueller, A.L.–Design, synthesis and biological evaluation of NPS 846 hydrochloride, a novel antagonist at the NMDA receptor. *212th National Meeting of the American Chemical Society*, ORGN 273, Orlando, Florida, August 25-29, 1996.
4. Artman, L.D.; VanWagenen, B.C.; Balandrin, M.F.; DelMar, E.G.; Hammerland, L.G.; Donovan, S.D.; Rogawski, M.A.; Williams, K.; and Mueller, A.L.–NPS 846·HCl, a novel open-channel blocker of the NMDA receptor: *in vitro* characterization. *Soc. Neurosci. Abstr.* 22, Part 2: 1282, 508.8 (1996).
5. Mueller, A.L.; Artman, L.D.; Li, H.; Balster, R.L.; Taylor, D.; and Parks, T.N.–NPS 846·HCl, a novel open-channel blocker of the NMDA receptor: *in vivo* characterization. *Soc. Neurosci. Abstr.* 22, Part 2: 1282, 508.9 (1996).

6. Chien, Y.; Raskiewicz, J.L.; Draper, S.; White, H.S.; and Mueller, A.L.–Neuroprotectant and anticonvulsant properties of NPS 846·HCl, a novel NMDA receptor antagonist. *Soc. Neurosci. Abstr.* 22, Part 2: 1282, 508.10 (1996).
7. Mueller, A.L.; Moe, S.T.; Balandrin, M.F.; Delmar, E.G.; Van Wagenen, B.C.; Artman, L.D.; Barmore, R.M.; and Smith, D.L.–Compounds active at a novel site on receptor operated calcium channels useful for treatment of neurological disorders: Preparation of 1-amino-3,3-diphenylpropanes and related compounds as noncompetative antagonists of glutamate receptor-operated calcium channels in the central nervous system. *PCT Internatl. Appl. WO* 96/40,097 (December 19, 1996); *U.S. Patent Appl.* 08/485,038 (June 7, 1995), 313 pp.; *Chem. Abstr.* 126: P 143970 (1995).
8. Watkins, J.E.; and Evans, R.H.–Excitatory amino acid transmitters. *Annu. Rev. Pharmacol. Toxicol.* 21: 165-204 (1981).
9. Foster, A.C.; and Fagg, G.E.–Acidic amino acid binding sites in mammalian neuronal membranes: Their characteristics and relationship to synaptic receptors. *Brain Res. Rev.* 7: 103-104 (1984).
10. Choi, D.W.–Glutamate neurotoxicity and diseases of the nervous system. *Neuron* 1: 623-634 (1988).
11. MacDermott, A.B.; Mayer, M.L.; Westbrook, G.L.; Smith, S.J.; and Barker, J.L.–NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurons. *Nature* 321: 519-522 (1986).
12. Schanne, F.A.; Kane A.B.; Young, E.E.; and Farber, J.L.–Calcium dependence of toxic cell death: A final common pathway. *Science* 206: 700-702 (1979).
13. Meldrum, B.S.; and Chapman, A.G.–Competitive NMDA antagonists as drugs. *In:* Collingridge G.L. and Watkins J.C. (Eds.), *The NMDA Receptor*, 2nd ed., Oxford University Press, NY, 1994, pp. 457-468.
14. Evans, E. A.–*Tritium and Its Compounds*, Van Nostrand Co., Princeton, NJ, 1966, pp. 139-144.
15. Marton, J.; and Kovacs, A.–Heterogenous catalytic exchange reaction between tritium gas and the solvent in the catalytic tritiation of saturated compounds. *Radioisotopy* 12(4), 595-604 (1971); see also [*Chem. Abstr.* 76: 104285 (1971)].
16. Hanus, J.; Cerny, B.; and Benes, J.–The [*sic*] tritium incorporation into the [*sic*] solvents under conditions of catalytic hydrogenation. *J. Labelled Compds.* 10: 523-531 (1974).
17. Silverstein, R.M.; Bassler, G.C.; and Morrill, T.C.–*Spectrometric Identification of Organic Compounds*, 5th ed., John Wiley & Sons, NY, 1991, p 10.

