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NOTE

PREPARATION OF HIGH SPECIFIC ACTIVITY [15,16-^{3}H]-7-BENZYLIDENENALTREXONE

Anita H. Lewin* and Pamela B. Lamb

Research Triangle Institute, P. O. Box 12194
Research Triangle Park, North Carolina 27709-2194 USA

*Author to whom correspondence should be addressed.

SUMMARY

The preparation of the δ_1-specific ligand 7-benzylidenenaltrexone (BNTX), labeled with tritium at high specific activity (14.4 Ci/mmol) was prepared in 33% yield and >98% purity by the aldol condensation of high specific activity [15,16-^{3}H]naltrexone with benzaldehyde at high dilution.

Key Words: 7-benzylidenenaltrexone (BNTX), tritium labeled, high specific activity, δ-selective opioid receptor antagonist

INTRODUCTION

High specific activity ligands are essential to carrying out radio-receptor binding studies. The recent development of potent nonpeptide δ-opioid antagonists (1) and, in particular, of 7-benzylidenenaltrexone (BNTX) (1), which has been characterized as a highly selective δ_1-opioid receptor antagonist (2) useful in probing δ-receptor subtypes (3), prompted us to undertake the preparation of high specific activity BNTX.

RESULTS AND DISCUSSION

The synthesis of high specific activity compounds resembling BNTX (1) has been accomplished by reductive dehalogenation of an appropriate halogenated analog, or by reduction of an enamine, under tritium gas. For example, high specific activity naltrindole has been prepared from the dibromo-analog (4) and high specific activity naltrexone has been prepared from 15,16-didehydronaltrexone (5). However, neither of these procedures is applicable to BNTX (1) due to the presence of the double bond in the benzylidene portion of the molecule. To prepare tritium labeled naloxone, which also possesses a double bond, exchange of the iminium ion of 15,16-didehydronaltrexone with tritium oxide followed by reduction with sodium cyanoborohydride, has been reported (5). This

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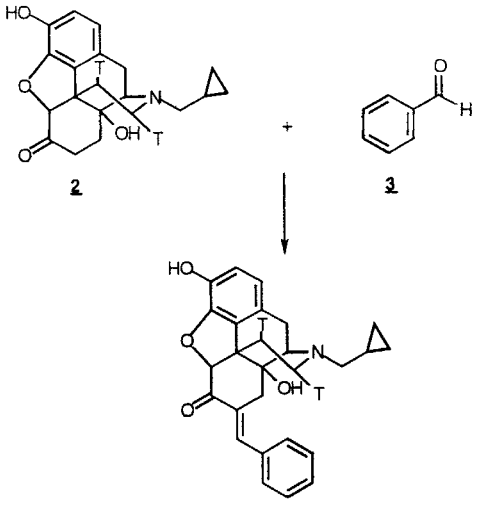
approach was rejected since it was not likely to produce material of sufficiently high specific activity (5) for receptor binding studies. It was, therefore, decided to prepare high specific activity BNTX (1) by the reported aldol condensation (1,6) utilizing high specific activity [15,16-^{3}H]naltrexone (2) (5) (Scheme).

Scheme



2 3 1

According to the reported procedure (1,6) a 63 mM solution of naltrexone in methanolic base was treated with excess benzaldehyde in the cold for 12 hours. For naltrexone of specific activity ~15 Ci/mol this would mean keeping a methanolic solution of 1 Ci/mL over a 12 hour period. Although our experience indicated that solutions containing such concentrated radioactivity undergo extensive decomposition, we attempted to carry out the reaction under these conditions. Starting with [15,16-^{3}H]naltrexone (2) of specific activity 14.4 Ci/mmol, prepared following the reported procedure (5), and a 7.5 fold excess of benzaldehyde (3) the condensation was carried out over a 17 hour period at 12°C; TLC-radioscan of the product mixture indicated that it consisted of 13% [15,16-^{3}H]BNTX (1), 42% [15,16-^{3}H]naltrexone (2) and 38% of a radioactive decomposition product. Repeating the reaction under conditions of 50 fold dilution with 50 fold excess of benzaldehyde (3) in a 1.5 mM solution afforded [^{3}H]BNTX (1) in 30% isolated yield (Scheme). This material was stable for approximately 6 months when stored in 30% ethanol/toluene (3:7) at a concentration of 0.59 mCi/mL.

EXPERIMENTAL SECTION

Thin layer chromatography (TLC) was carried out on Whatman silica gel 60 plates using $CHCl_3$:CH_3OH:acetone (19:0.5:0.1) as the eluant. Visualization was accomplished using UV. TLC-radioscan analyses were performed using a Berthold Automatic TLC-Linear Analyzer. Samples were

counted in an Ultima Gold scintillation cocktail on a Packard Tri-Carb 400 Series liquid scintillation counter. Naltrexone hydrochloride and unlabeled BNTX (7) were obtained from the NIDA Drug Supply Program.

[15,16-^{3}H]7-Benzylidenenaltrexone ([^{3}H]BNTX) (1). To a cooled solution of [15,16-^{3}H]-naltrexone (**2**) (66 mCi, 4.58 μmol) in CH_3OH (2 mL) was added 1N NaOH (1 mL) and benzaldehyde (**3**) (30 μL, 250 μmol). This solution was refrigerated for 22 h, then diluted with H_2O (4 mL), acidified with 1N HCl and washed with $CHCl_3$. The aqueous phase was then basified with NH_4OH and extracted with $CHCl_3$ (5 x 25 mL). After drying over Na_2SO_4, the solvent was evaporated and the residue was purified by pTLC [20 x 20 cm, 0.25 mm F-254 SiO_2; $CHCl_3$:CH_3OH:acetone (19:0.5:0.1)] to afford 20.0 mCi of tritiated BNTX (**1**) (R_f 0.66) with specific activity 14.4 Ci/mmol (12.2 mCi/mg). Unreacted **2** (R_f 0.57) was also recovered (4.9 mCi, 7.5%).

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