SYNTHESIS OF TRITIUM LABELED NADOLOL

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SUMMARY

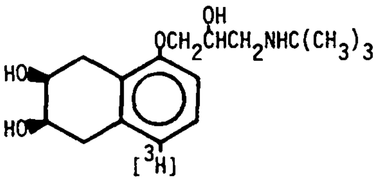
Tritium labeled nadolol (3) was prepared by electrophilic bromination of nadolol (1) to give 8'-bromonadolol (2). Catalytic reductive debromination with tritium gas gave 8'-[^{3}H]-nadolol (3), with a specific activity of 3.36 Ci/mmol.

Key Words: 8'-Bromonadolol, Nadolol

INTRODUCTION

Nadolol, a new beta adrenergic receptor antagonist, has recently become available in the U.S. This drug has been shown to be useful in the treatment of hypertension[1] and angina.[1,2] But unlike propranolol, nadolol neither causes myocardial depression[3,4,5] nor is it metabolized.[6,7]

In order to further investigate the pharmacology of this useful agent we required radiolabeled nadolol. In this note we report the synthesis of 8'-[^{3}H]-nadolol (3).



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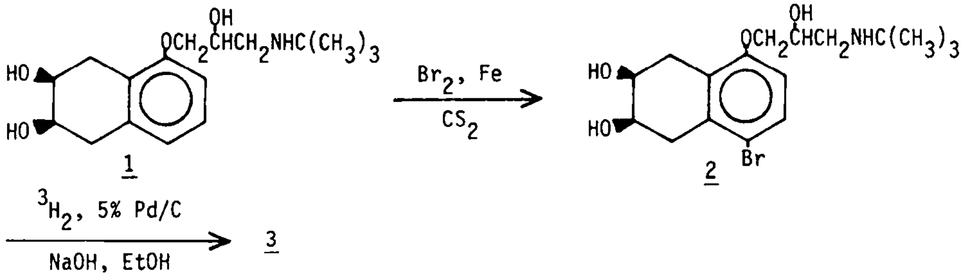
RESULTS AND DISCUSSION

Although acid catalized exchange has been employed to prepare 2,4-dideutero propranolol,[8] it was decided that this procedure is incompatible with the two ring hydroxyl groups in nadolol. In an alternative route 8'-bromonadolol is prepared in excellent yield by electrophilic bromination of nadolol. Reductive debromination with tritium gas over palladium on carbon followed by purification on HPLC gave the desired 8'-[^{3}H]-nadolol (3).



EXPERIMENTAL

PMR spectra were obtained in $CDCl_3$ at ambient temperature using tetramethylsilane as internal standard on a Varian T60 NMR spectrometer. Electron impact mass spectra were obtained at 70 eV on a Finnigan 3200 GC/MS interfaced with a Finnigan 6000 data system. Both NMR and MS spectra are consistent with assigned structures. UV spectra were recorded on a Cary-15 scanning spectrophotometer. Radioactivity measurements were made on a Beckman LS355 liquid scintillation counter using ACS, Amersham counting fluid. The yield of 3 was calculated using the extinction coefficient of 1, while the specific activity of 3 was obtained by counting an aliquot of 3. HPLC was performed on a Waters Associates M-6000A pump, a Valco injector, and a Varian variable wavelength detector at 280nm using either 4.6 mm x 25 cm Zorbax ODS or a 50 cm Whatman M-9 ODS-2 column with 0.1 M NH_4OAc-CH_3CN (7:3) as eluent. The reductive tritiation was done at New England Nuclear, Boston, Mass.

8'-Bromonadolol (2) To nadolol (25.2 mg, 814 µmole) and iron powder suspended in CS_2 (100 µL) and cooled in an ice bath was added Br_2 (5 µL, 15.6 mg, 976 µmoles) dissolved in CS_2 (40 µL). The reaction mixture was stirred at 0°C for 4 hrs, at which time HPLC K' (2) = 11.8, K' (1) = 5.7 showed the reaction to be complete. After removal of the solvent in a stream of N_2, the residue was dissolved in the HPLC solvent, filtered using a syringe millipore filter and the filtrate chromatographed on the 50 cm M-9 column. The fraction containing the product was lyophillized, the residue dissolved in H_2O (20 mL), basified (pH 11) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated to yield 30.2 mg (95.6% yield) of 2 as a white solid. NMR ($CDCl_3$) δ 1.12 (s,9,$C(CH_3)_3$), 2.6-3.2 (m,6, CH_2N, benzylic), 3.23 (bs,4,OH, NH), 3.6-4.4 (m,5,CH_2CHO,CHOHCHOH), 6.52 (d,J=9 Hz, 1, H-6'), 7.33 (d, J=9 Hz, 1, H-7'). MS (tris-trimethylsilyl derivative), m/z 603, 605 (M^+) 588,590 ($M-CH_3$), 386,388 ($M-CH_3-CH_2CH(OSiMe_3)CH_2NHC(CH_3)_3$, 86 ($CH_2{=}NHC(CH_3)_3^+$), 73 ($SiMe_3$).

8'-[^{3}H]-nadolol(3) 2 (1 mg 2.58 µmole) dissolved in EtOH (1 mL) containing NaOH (0.1 mg, 2.5 µmole) and 5% Pd/C (5 mg) was stirred at room temperature overnight in an atmosphere of $^3H_2$ gas. Labile tritium was removed in vacuo using EtOH as solvent. After filtration from the catalyst, the product was again taken to dryness in vacuo. The product was purified on the analytical HPLC, to yield 69.9 µg of 2, specific activity 3.36 Ci/mmol. Both uv and K' for 3 were identical to those of 1. UV (in 95% ethanol) λ max nm (ε): 217(7210), 269(1000), 277(1030).

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