SYNTHESIS OF RACEMIC AMPHETAMINE-d_1 AND AMPHETAMINE-d_3

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SUMMARY

The synthesis of racemic amphetamine-d_1 and amphetamine-d_3 is described. Low temperature reduction of benzoyl chloride with lithium deuterido-tri(t-butoxy)-aluminate afforded the desired benzaldehyde-d_1 in good yield. The aldehyde was condensed with nitroethane and the resulting phenyl-2-nitropropene-d_1 was reduced with $LiAlH_4$ to give racemic amphetamine-d_1, or with $LiAlD_4$ to furnish racemic amphetamine-d_3 in approximately 50% overall yield.

Key Words: Amphetamine, Deuterium Labelling, Lithium Deuterido-tri(t-butoxy)aluminate, Reduction.

INTRODUCTION

In an investigation designed to study the effect of deuteration of amphetamine on spontaneous locomotor activity in mice, it became necessary to prepare racemic amphetamine-d_1 (4a) and amphetamine-d_3 (4b). These isotopically labelled analogs of amphetamine have not been heretofore reported and therefore a selective synthesis which would produce the desired amphetamine analogs was sought. One of the most direct methods for preparing phenylethylamine derivatives is the use of a nitroalkene as an intermediate which can be readily prepared by the base-catalyzed condensation of the appropriate aromatic aldehyde and nitroalkane.

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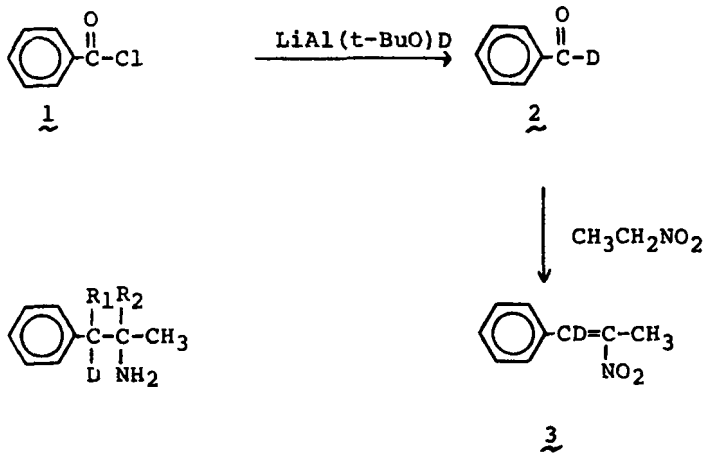
A number of chemical syntheses have been reported for the preparation of non-deuterated benzaldehyde (1). However, the procedure of Brown and McFarlin (2) as modified by Blackburn and Burguard (3) for the low temperature reduction of benzoyl chloride to benzaldehyde with lithium hydrido-tri(t-butoxy)aluminate/ ($LiAl(t\text{-}BuO)_3H$ / in tetrahydrofuran (THF) appeared to be the simplest and, hence, it was employed for the preparation of the desired benzaldehyde-d_1 (2). Lithium deuterido-tri(t-butoxy)aluminate / ($LiAl(t\text{-}BuO)_3D$ / was easily prepared by the reaction of three moles of t-butyl alcohol with 1 mole of lithium tetradeuteridoaluminate ($LiAlD_4$) in anhydrous ether. Benzaldehyde-d_1 prepared by the above procedure, was treated with excess nitroethane in benzene under reflux and in the presence of piperidine and n-butylamine as basic catalysts. The water formed as a by-product of the reaction was removed with the aid of a Dean Stark trap (4). Subsequent evaporation of solvent benzene from the reaction mixture afforded 1-phenyl-2-nitropropene-d_1 (3) in excellent yields. The resulting nitroalkene (3) was then reduced to dl-phenyl-2-aminopropane-d_1 (4a) with $LiAlH_4$ in anhydrous ether or to dl-phenyl-2-aminopropane-d_3 (4b) with $LiAlD_4$ in anhydrous ether as depicted in scheme I.



4a $R_1=R_2=H$

4b $R_1=R_2=D$

SCHEME I

The advantages of the above synthesis include its simplicity, the availability of $LiAlD_4$ or $LiAl(t\text{-}BuO)_3D$ as a convenient source of deuterium, and the high overall yield.

With the rapid expanding application of GC/MS in biomedical sciences (5-7), these deuterioanalogs of amphetamine should prove useful in studying the pharmacokinetics of amphetamine, the mechanism of its detoxification *in vivo* and *in vitro* and in other areas of biomedical research related to pharmacological, toxicological and behavioral actions of amphetamines.

EXPERIMENTAL

Melting points were determined with a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60A spectrometer in chloroform-d with tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6D GC/MS. IR spectra were obtained on a Perkin-Elmer 257 Grating Infrared Spectrophotometer. $LiAlD_4$ was purchased from Merck, Sharp and Dohme Canada Ltd. THF was purified by distillation from $LiAlH_4$ immediately before use. Micro-analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Lithium deuterido-tri(t-butoxy)aluminate - To a well stirred suspension of $LiAlD_4$ (2.52 g, 60 mmol) in anhydrous ether (150 ml) in a 500 ml round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser with a calcium chloride drying tube on top, a solution of freshly distilled anhydrous t-butyl alcohol (13.83 g, 189 mmol) in anhydrous ether (60 ml) was added at such a rate as to maintain gentle reflux. The reaction mixture was stirred for an additional 15 minutes at room temperature after all of the alcoholic solution was added. The solvent and excess t-butyl alcohol were then removed affording 13.1 g (86%) of desired $LiAl(t\text{-}BuO)_3D$.

Benzaldehyde-d_1 (2) - A slurry of $LiAl(t\text{-}BuO)_3D$ (13.1 g, 51.4 mmol) in anhydrous THF (50 ml) was added to a well-stirred solution of benzoyl chloride (6.85 g, 48.7 mmol) in dry THF (21 ml) maintained at -78°. The mixture was stirred for 1 hr. at -78° and brought to room temperature by removing the dry-ice bath. The mixture was then poured into crushed ice (100 g) and the products were extracted several times with ether. The ether and THF were removed in vacuo and the residue was redissolved in ether (100 ml) and washed twice with water (60 ml) to remove any trace of THF. The ethereal solution was then dried (anhyd. $MgSO_4$) filtered and evaporated to dryness yielding 5.1 g of crude 2. The crude benzaldehyde-d_1, was purified by converting to the bisulfite addition compound with 40% sodium bisulfite solution. The solid collected was filtered, washed with ether and re-converted to 2 with 10% sodium bicarbonate solution. Extraction with ether, dried (anhyd. $MgSO_4$), filtered and removal of solvent affords 3.9 g (74%) of pure 2 as colorless liquid. IR (neat, cm^{-1}) 2100 and 2050 (C-D stretching), 1680 (C=O); NMR δ 7.42 - 7.92 (m, 5, ArH).

1-Phenyl-2-nitropropene-d_1 (3) - A solution of 2 (2.5 g 23.4 mmol), nitroethane (2.55 ml), piperidine (0.177 ml), n-butylamine (0.12 ml) in benzene (50 ml) was placed in a round-bottomed flask equipped with reflux condenser and a Dean Stark trap. The mixture was refluxed for 11 hr and the water formed was removed by the trap. The excess nitroethane and benzene were removed in vacuo. The residue was redissolved in ether, washed twice with water, dried (anhyd. $MgSO_4$),

filtered and evaporated in vacuo to furnish 3.4 g (88.6%) of 3 as crude oil which crystallized upon standing. Recrystallization from ethanol afforded yellow needle-like crystals, mp. 64° (lit. (8) for unlabelled 3, mp. 64-65°); IR (KBr, cm^{-1}) 1625 (C=C), 1510 and 1320 (NO_2). NMR δ 2.42 (s, 3, CH_3), 7.4 (s, 5, ArH). Anal. Calcd for $C_9H_8DNO_2$: C, 65.84; H, 4.91; D, 1.23; N, 8.53. Found, C, 65.82; H, 4.88; D, 1.22; N, 8.54.

dl-phenyl-2-aminopropane-d_1 (4a) - A solution of 3 (2.0 g, 12 mmol) in anhydrous ether (60 ml) was added with stirring to a refluxing slurry of $LiAlH_4$ (1.34 g, 35.3 mmol) in anhydrous ether (30 ml). The mixture was refluxed for 2 hr and the excess hydride was decomposed by successive dropwise addition of 10% NaOH (2 ml) and water (3 ml). The insoluble salt was removed by filtration, washed with anhydrous ether, and the combined filtrate and washing were concentrated in vacuo and extracted with 10% HCl. The acidic aqueous layer was separated and washed twice with CH_2Cl_2 and then made alkaline with 10% $NaHCO_3$. The pale yellow oil which separated was extracted into ether, dried (anhyd. $MgSO_4$) filtered and the solvent removed in vacuo affording 1.27 g (78%) of 4a as pale yellow oil which was converted immediately to the sulfate salt by the addition of ethereal sulfuric acid to the cold ethereal solution of the amine. Recrystallization of the sulfate salt from aqueous ethanol yielding 1.0 g of 4a, mp. 310° decomp. (lit. (8) mp. 300° decomp. for the unlabelled analogs); IR (KBr, cm^{-1}) 3360 and 3270 (NH_2) 2270 (C-D); NMR δ 1.1 (d, 3, CH_3), 1.42 (s, 2, NH_2), 7.2 (s, 5, ArH),

2.55 (m, 1, $ArC\underline{H}D$), 3.1 (m, 1, $CH_3C\underline{H}NH_2$); MS m/e 92 ($C_6H_5CHC^+$), 44 ($CH_3CH{=}NH_2^+$). Anal. calcd for $C_{18}H_{26}D_2N_2SO_4$: C, 58.35; H, 7.07; D, 1.09; N, 7.56. Found, C, 58.37; H, 6.85; D, 1.05; N, 7.52.

dl-Phenyl-2-aminopropane-d_3 (4b) - It was prepared in a manner similar to 4a from 3 (3.0 g, 18.3 mmol) and $LiAlD_4$ (2.0 g, 47.6 mmol) in anhydrous ether. The crude amine 4b obtained (1.9 g, 78% yield) was converted to its sulfate salt affording 1.7 g of pure 4b, mp 310° decomp. (recrystallized from EtOH-H_2O), IR (KBr, cm^{-1}) 3360 and 3270 (NH_2), 2270 (C-D); NMR, δ 1.0 (s, 3, $C\underline{H}_3$), 2.8 (s, 2, $N\underline{H}_2$), 7.2 (s, 5, $Ar\underline{H}$). MS m/e 93 ($C_6H_5CD_2^+$) and 45 ($CH_3CD{=}NH_2^+$). Anal. calcd for $C_{18}H_{22}D_6N_2SO_4$: C, 57.60; H, 5.91; D, 3.44; N, 7.46. Found, C, 57.99; H, 5.80; D, 3.17; N, 7.69.

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