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SYNTHESIS OF FLUTAMIDE-d_7 AND ITS MAIN METABOLITE-d_6

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SUMMARY

With the main objective of examining the pharmacokinetics of flutamide, flutamide-d_7 and its main metabolite-d_6 have been prepared. By carboxylation of Grignard-derivative (IV), deuterocarboxylic acid (V) was prepared from which acyl chloride (VI) was obtained by reaction with $(COCl)_2$. Subsequent reaction of (VI) with 4-nitro-3-trifluoromethylaniline afforded (I). Compound (X) was obtained starting from hydroxyacid (IX), through reaction with TMSCl, $(COCl)_2$ and subsequent condensation with 4-nitro-3-trifluoromethylaniline. Desilylation of (X) by tetrabutylammonium fluoride, gave (II).

Key words: Flutamide: Flutamide-d_7; Flutamide-Metabolite-d_6;
2-hydroxypropanoic- d_6 acid; propanoic- d_7 acid; acetonecyanohydrin- d_6

INTRODUCTION

Flutamide is a nonsteroidal compound reported to inhibit the uptake of binding of androgens in target tissues (1) Analysis of plasma urine and feces, following a single oral 250 mg dose to human volunteers showed that the drug is rapidly and completed absorbed. The analysis of plasma showed that flutamide is rapidly and extensively metabolized - at least six metabolites have been identified in plasma (2,3). The major metabolite is a biologically active alpha-hydroxylated compound which accounts for 23% of the plasma tritium (using tritiated flutamide) 1 hour after drug administration (3). With the aim of investigating the pharmacokinetics of flutamide we prepared the deuterated compounds (I) and (II).

DISCUSSION

Propanoic acid-d_7 (V) was prepared starting from 2-bromopropane (III), via Grignard (IV). Reaction of (V) with trimethylsilyl chloride (TMSCl) followed by treatment with oxalyl chloride furnished the corresponding acyl derivative (VI) that was immediately reacted with 4-nitro-3-trifluoromethylaniline in the presence of pyridine.The isolated compound (I) (Scheme I) was obtained in 48% total yield.

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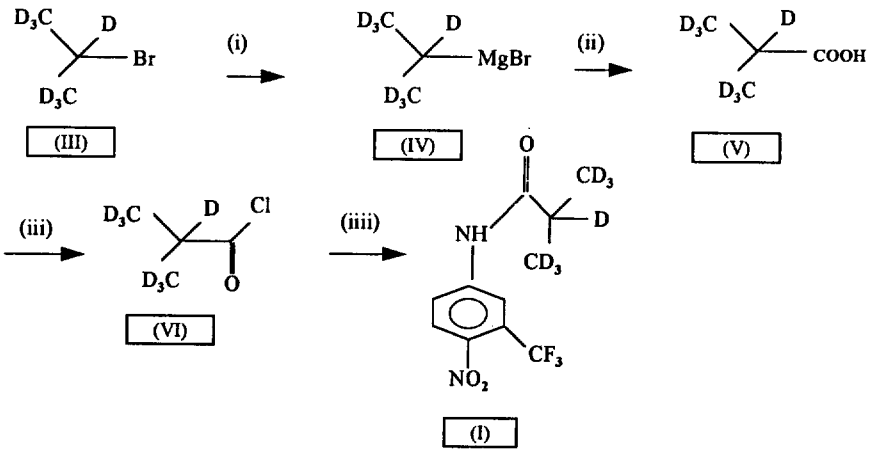
Acetonecyanohydrin-d_6 (VIII) (obtained from acetone-d_6 by reaction with trimethylsilyl cyanide) (Scheme II) was hydrolyzed to 2-hydroxyisobutyric-d_6 acid (IX). Reaction of (IX) with trimethylsilyl chloride and oxalyl chloride, followed by amidation with 4-nitro-3-trifluoromethylaniline, gave the silyl-derivative (X) Quantitative deprotection of the hydroxy group with tetrabutylammonium fluoride, resulted in the formation off (II)(17% total yield)

SCHEME - 1



(i) Mg; tetrahydrofuran (THF)

(ii) CO_2

(iii) trimethylsilyl chloride (TMSCl), 4-dimethylaminopyridine (DMAP), oxalyl chloride $(COCl)_2$

(iiii) 4-nitro-3-trifluoromethylaniline

EXPERIMENTAL

2-Methyl-d_3-propanoic-2,3,3,3-d_4 acid (V)

5.6 g of Magnesium (0.2 mol) was dry stirred under a nitrogen atmosphere for 15 h. Tetrahydrofuran (THF) (60ml) was added and the resulting black suspension was cooled to -20°C. A solution of 2-bromopropane-d_7(III)(5g, 38 mmol) in THF (60ml) was added dropwise maintaining the bath temperature at -20°C. The suspension was stirred for 1 h at -20°C. The bath was cooled to -70°C and an excess of solid CO_2 was added (4). The mixture was allowed to warm to room temperature, filtered and evaporated. The residue was dissolved in an acqueous sodium hydrogen carbonate solution (5%) and washed with ether .
The aqueous solution was then acidified with diluted aqueous HCl and extracted with Et_2O (3 x 25m). The solvent was removed under reduced pressure to give (V) (2g; 55%).

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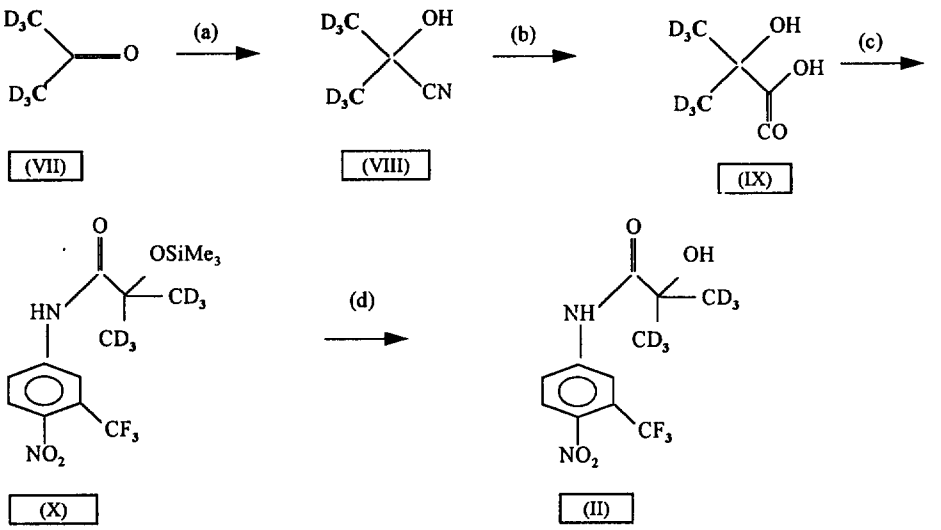
SCHEME - 2



(a): trimethylsilyl cyanide (TMSCN), $ZnCl_2$

(b): H_2SO_4 25%

(c): trimethylsilyl chloride (TMSCl), 4-dimethylaminopyridine (DMAP); oxalyl chloride $(COCl)_2$ 4-nitro-3-trifluoromethylaniline

(d): tetrabutylammonium fluoride (TBAF), tetrahydrofuran (THF)

2-Methyl-d_3-N-(4-nitro-3-trifluoromethylphenyl)propanamide-2,3,3,3-d_4 (I)

To a solution of (V) (2g, 21 mmol), 4-dimethylaminopyridine (DMAP) (5 mg 0.04 mmol) and pyridine (3 ml, 43 mmol) in CH_2Cl_2(36 ml) trimethylsilyl chloride (TMSCl) was added (3 ml, 22 mmol) dropwise. The reaction was stirred at room temperature for 4 h. The reaction was then cooled to 0°C and DMF (20µl) was added followed by oxalyl chloride (1.8 ml, 21 mmol). The reaction was stirred for 1 h at 0°C and then 30 min at room temperature. A solution of 4-nitro-3-trifluoromethylaniline (4.5g, 21 mmol) in pyridine (4.8 ml) was added at 0°C and the reaction was allowed to warm to room temperature. After 2 h a solution of citric acid (4.16g, 20 mmol) in methanol (35 ml) was added . After 30 min., the reaction was poured into a separatory funnel and diluted with EtOAc (40 ml). The organic phase was washed with 1 N HCl (40 ml) and the aqueous layer was back extracted with ethyl acetate (20ml). The combined organic layers were washed firstly with saturated bicarbonate solution (20 ml) then with brine (saturated aqueous solution) (20 ml) and dried (Na_2SO_4). After solvent removal (I) was obtained as a yellow solid (2.6 g, 10 mmol 48%) . mp: 102°C (5)

$C_{11}H_4N_2F_3O_3D_7$

^{1}H-NMR: ($CDCl_3$) (δ,ppm) 8.04 (1H, sb); 8.03 (1H, d, *J*=5Hz); 8.02 (1H, d, *J*=5Hz); 7.62 (1H, s).

^{13}C-NMR: ($CDCl_3$) (δ,ppm) 176.54; 142.79; 142.46; 126.91; 125.31; 124.43; 122.17; 118.32; 35.46 (m); 19,10 (2C,m)

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2-Cyano-2-propanol-1,1,1,3,3,3-d_6 (VIII)

A solution of acetone-d_6 (10 ml; 136 mmol), trimethylsilyl cyanide (TMSCN) (15.7 g; 158 mmol), anhydrous $ZnCl_2$ (500 mg; 4 mmol) and 50 ml of CH_2Cl_2 was heated at 60°C. After 3h the solvent was evaporated and the crude product, O-(trimethylsilyl)deuteroacetone cyanohydrin, was dissolved in 40 ml of THF and 25 ml of 3 N HCl. The mixture was heated at 65°C for 2 hours. On cooling the solution was poured into a separatory funnel and washed with a 3 N NaOH (35 ml). The aqueous phase was separated and extracted with EtOAc. (20 ml) The organic layers were combined with the tetrahydrofuran solution and dried (Na_2SO_4), filtered and evaporated to give 9.8 g of product. (108 mmol 80%)
IR ($CHCl_3$) υ_{max} 3000 (s); 2240 (s).

2-Hydroxy-2-methyl-d_3-propanoic-3,3,3-d_3 acid (IX)

25% H_2SO_4 (20 ml) was added to a solution of deuteroacetone cyanohydrin (VIII) (9g, 98 mmol) in 20 ml of H_2O. The mixture was heated at 50°C for 2 days. The solution was cooled and 30 ml of saturated brine solution (2 x 20 ml) was added , then the mixture was extracted with Et_2O (3 x 30ml).
The organic layers were dried with Na_2SO_4 and concentrated to give the product (9g, 82 mmol 84%). IR ($CHCl_3$) ν_{max} 3000(cm^{-1}) ; 1710 (cm^{-1})

2-Methyl-d_3-N-(4-nitro-3-trifluoromethylphenyl)-2-trimetylsilyloxy.propanamide-3,3,3-d_3 (X).

To a solution of (IX) (2 g, 18 mmol), 4-dimethylaminopyridine (DMAP) (5 mg 0.04 mmol) and pyridine (2.9 ml, 37 mmol) in CH_2Cl_2 (36 ml) trimethylsilyl chloride (TMSCI) (5 ml, 38 mmol) was added dropwise. The reaction was stirred at room temperature for 4 h. The reaction was cooled to 0°C and DMF (20µl) was added followed by oxalyl chloride (1.6 ml, 18 mmol). The reaction was stirred for 1h. at 0°C and then 30 min. at room temperature. A solution of 4-nitro-3-trifluoromethyl aniline (4g, 20 mmol) in pyridine (4.8 ml) was added at 0°C and the reaction was allowed to warm to room temperature. After 2 h a solution of citric acid (4.16g, 20 mmol) in methanol (35 ml) was dropped. After 30 min. the reaction mixture was poured into a separatory funnel and diluited with EtOAc (40 ml). The organic phase was washed with 1 N HCl (40 ml) and the aqueous solution was back extracted with EtOAc (20 ml). The combined organic layers were firstly washed with $NaHCO_3$ (20 ml, 5%) then with saturated brine solution (20 ml) and dried (Na_2SO_4). The product obtained upon concentration was purified by chromatography on silica gel (EtOAc/hexane 4:1) to give 2.9 g of (X) (44%) and 1g of (I) (17%).

$C_{14}H_{13}O_4Si_1N_2D_6F_3$
Rf (EtOAc/Hexane 4:1): 0.4

^{1}H-NMR ($CDCl_3$, , 200 MHz): (δ ppm) 9.18 (1H, sb); 8.11 (1H, d, *J*=2 Hz); 7.98 (1H, d, *J*= 8Hz); 7.90 (1H, dd, *J*=8,2 Hz); 0.25 (9H, s)

2-Hydroxy-2-methyl-d_3-N-(4-nitro-3-trifluoromethylphenyl) propanamide-3,3,3-d_3 (II)

To a solution (X) (2.9g, 8 mmol) in 40 ml of tetrahydrofuran was added tetrabutylammonium fluoride (2.2g, 8 mmol). Water (50 ml) was added to the mixture and the aqueous phase was extracted with EtOAc (2 x 50 ml). The organic phase was concentrated to give 2.2 g of (**II**) (8mmol).
mp 120°C

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$C_{11}H_{13}O_4Si_1N_2D_6F_3$
Rf (EtOAc/Hexane 4:1): 0.2
^{1}H-NMR ($CDCl_3$, rt, 200 MHz): (δ ppm) 9.25 (1H, sb); 9.15 (1H, s); 8.01 (1H, d, *J*=8 Hz); 7.95 (1H, d, *J*= 8Hz); 4.04 (1H, s).
^{13}C-NMR: ($CDCl_3$, 50,2 Mhz), δ (ppm) : 176.5 142.82; 142.40; 126.77; 125.53; 124.05; 121.96; 118.18, 78.12; 19.10 (2C, m).

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