ScienSage

Journal of Advanced Scientific Research

Available online through http://www.sciensage.info/jasr

ISSN
0976-9595
Short Communication

IODINATION OF PARACETAMOL

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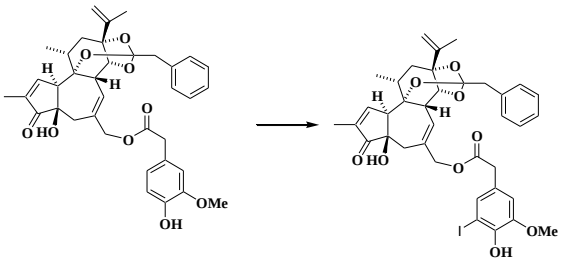
ABSTRACT

Iodoresiniferatoxin (I-RTX) is a strong competitive antagonist of the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor. However, resiniferatoxin itself, as a painkiller substance, is a TRPV1 receptor agonist. As paracetamol has also a painkiller action of low intensity, its iodination can have a reverse effect.

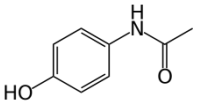
Keywords: Iodoresiniferatoxin (I-RTX), TRPV1 receptor, Iodoparacetamol, Painkiller action, Antagonist.

1. INTRODUCTION

Resiniferatoxin (RTX) (**1**) is a plant substance present in the latex of Euphorbia resin canal [1], and it is now used as anti-pain treatment. Its action is comparable to capsaicin, but 1000 times more powerful [2, 3]. The previous work carried out on the iodination of some molecules with anti-pain effect, especially on resiniferatoxin, showed the inversion of the pharmacological activity of resiniferatoxin from agonist to antagonist [4-8]. We were inspired by this work, and that's why we have undertaken, as an objective of our present work, the iodination of paracetamol (**3**) which is also an anti-pain drug but of lower potency than resiniferatoxin.



1 **2**



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2. RESULTS AND DISCUSSION

In our present work, 3-iodoparacetamol (4-acetamido-3-iodophenol) (**8**) could be prepared using 4-aminophenol as a starting material. Thus, a methanolic solution of 4-aminophenol (**4**) was treated with di-tert-butyldicarbonate (Boc_2O) in the presence of triethylamine to give the 4-Boc-amino-1-Boc-phenol (**5**). The latter compound was then reacted with iodine in the presence of silver trifluoroacetate to give the monoiodo compound 4-Boc-amino-3-iodo-Boc-phenol (**6**). Then compound (**6**) was deprotected by treatment of its solution in dichloromethane with trifluoroacetic acid to give 4-amino-3-iodophenol (**7**) which was finally reacted with acetic anhydride in the presence of triethylamine and pentaphosphoric acid anhydride to give the 3-iodoparacetamol (**8**).

On the other hand, it deemed of interest to prepare the other iododerivative of paracetamol namely 2-iodoparacetamol (**12**). Thus, the diazonium chloride of 4-aminobenzenesulfonic acid (**10**) was coupled with 2-iodophenol (**9**) in the presence of sodium hydroxide to give the intermediate azo compound **10a**. The latter compound was then reduced using sodium dithionite in the presence of sodium hydroxide to give 4-amino-2-iodophenol (**11**). Acetylation of compound **11** by treatment with acetic anhydride in dichloromethane in the presence of triethylamine and pentaphosphoric acid anhydride gave the target 2- iodoparacetamol (**12**).

3. EXPERIMENTAL

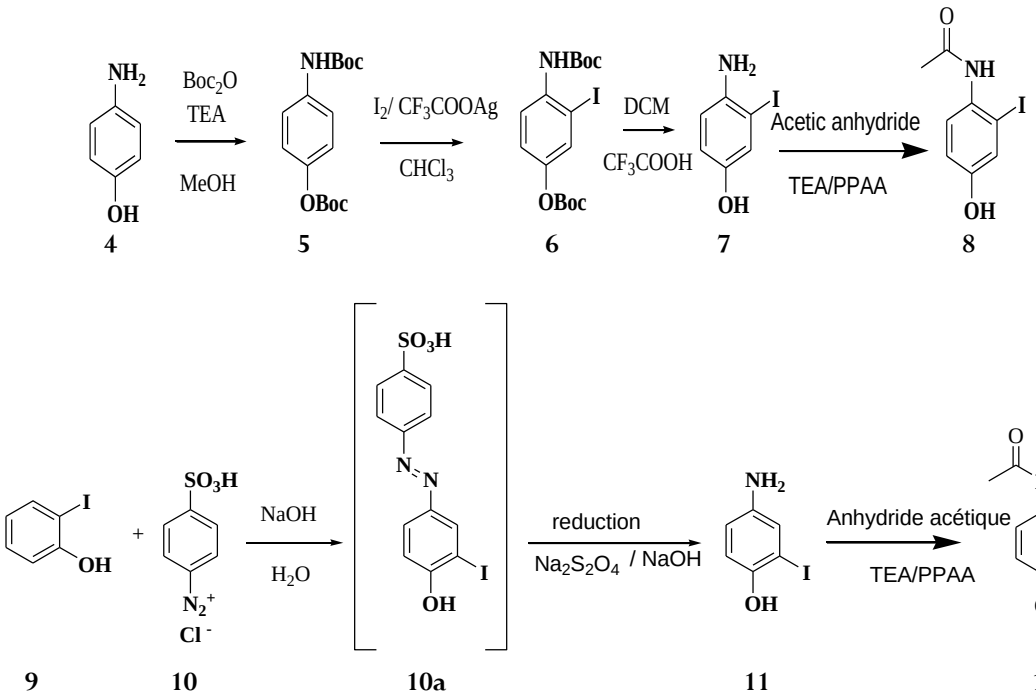
3.1. Preparation of 4-Boc-amino-Boc-phenol (5)

To a solution of 4-aminophenol (**4**) (1g, 9. 16 mmol), dissolved in 10 ml of methanol, di-tert-butyldicarbonate (Boc_2O) (4 g, 18.32 mmol) was added followed by 2 equivalents of triethylamine (18.35 mmol). The reaction mixture was heated under stirring at 45°C for 30 minutes. Stirring was continued for further 4 hours at room

temperature, and then the solvent was removed at reduced pressure. The residue obtained was dissolved in ethyl acetate (100 ml) followed by addition of 50 ml of 2N sulfuric acid solution, then the mixture is stirred at room temperature for few minutes. The organic phase was separated, washed, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The purification of the residue was done by silica gel chromatography using petroleum ether / ethyl acetate (80:20) as an eluent to give 2.2 g of 4-Boc-amino-Boc-phenol **(5)** in the form of a white solid, m.p. 45°C, yield 2.2 g (77.74%).

IR (cm^{-1}) : 3100 (NH), 1710 (C = 0), 1680 (C = O); ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ ppm = 7.61 (m, 2H, H_3 and H_5), 7.05 (m, 2H, H_2 and H_6), 1.40 (m, 18H); ^{13}C-NMR ($CDCl_3$, 75 MHz) : δ ppm = N-Boc : 153.9 (C=O), 79.5 (O-C-), 28.5 $(CH_3)_1$, 28.5 $(CH_3)_2$, 28.5 $(CH_3)_3$; OBoc : 152.6 (C=O), 86.2 (O-C'-), 28.5 $(CH_3)_1$', 28.5 $(CH_3)_2$', 28.5 $(CH_3)_3$', 132.7 (C_1), 122.0 (C_2), 121.8 (C_3), 147.0 (C_4), 121.8 (C_5), 122.0 (C_6); CI- EIMS : m/z [M + H $^+$] 310 [$C_{16}H_{23}NO_5$ + H].

3.1.1. Reaction scheme



3.2. 4-Boc-amino-3-iodo-Boc-phenol (6)

A mixture of compound **5** (0.5 g, 1.616 mmol), 1.1 equivalents of iodine (0.451 g, 1.777 mmol) and silver trifluoroacetate (0.392 g, 1.775 mmol) in chloroform (5 ml) was stirred at room temperature for 2 hours. The mixture is then filtered and taken up in 50 ml of water and 30 ml of ethyl acetate. The organic layer was separated, washed with saturated sodium sulfite then with sodium bicarbonate solution. The organic phase was dried over sodium sulfate, filtered and then evaporated under reduced pressure. The residue obtained was purified by column chromatography on silica gel using hexane /ethyl acetate (90:10) as an eluent to give brown crystals, m.p. 52 °C, yield 0.32 g (45%).

IR (cm^{-1}): 3100 (NH), 1700 (C = 0), 1680 (C = O); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm = 7.61 (s, H_2), 8.05 (s, H_5), 7.16 (s, H_6), 1.49-1.57 (18H); ^{13}C-NMR ($CDCl_3$, 75 MHz) : δ ppm = N-Boc : 154.7 (C=O), 70.5 (O-C-), 28,6 $(CH3)_1$, 28,6 $(CH3)_2$, 28,6 $(CH3)_3$, O-Boc : 148.6 (C=O), 77.4 (O-C'-), 28,6 $(CH_3)_1$', 28,6 $(CH_3)_2$', 28,6 $(CH_3)_3$', 143.7 (C_1), 89.4 (C_2), 130.3 (C_3), 150.1(C_4), 120.3 (C_5), 122.2 (C_6); CI- EIMS : m/z [M + H+436 [$C_{16}H_{22}INO_5$ + H].

3.3. 4-Amino-3-iodophenol (7)

Compound **6** (0.486 g, 1.116 mmol) was dissolved in trifluoroacetic acid (5 ml of a 5% solution of acid in dichloromethane) and the resulting solution was stirred at room temperature for overnight. The solvent was then evaporated and the solid residue obtained was purified by silica gel column chromatography using petroleum ether / ethyl acetate (60:40) as an eluent to give brown crystals, m.p. 41°C, yield 0.150 g (57%).

IR (cm^{-1}): 3300 (NH), 3400 (NH); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ ppm = 7.37 (s, 1H, H_2), 6.88 (d, 1H, H_5), 6.03 (d, 1H, H_6), 5.30 (m, 1H, OH), 4.20 (m, 2H, NH_2); ^{13}C-NMR ($CDCl_3$, 75 MHz) : δ ppm = 142.6 (C_1), 85.3 (C_2), 123.3 (C_3), 150.1 (C_4), 115.6 (C_5), 119.3 (C_6); CI- EIMS : m/z [M + H$^+$] 236 [C_6H_6INO + H].

3.4. 4-Acetamido-3-iodophenol (8)

A mixture of acetic anhydride (0.426 ml, 4.506 mmol), anhydrous dichloromethane (3 ml), triethylamine (0.429 ml,

3.072 mmol), a 50% solution pentaphosphoric acid anhydride in ethyl acetate (0.643 ml, 1.152 mmol) was stirred for 30 minutes then 4-amino-3-iodo phenol (0.361g, 1.536 mmol) was added. The reaction mixture was stirred at room temperature for overnight. After extraction with 20 ml of ethyl acetate, the organic phase was separated, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The solid residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (80:20) as an eluent. Evaporation of the solvent gave 4-acetamido-3-iodophenol (**8**) as brown oil, yield 0.180 g (45%).
IR (cm^{-1}): 3380 (NH), 1670 (C = O); ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ ppm = 7.81 (s, H_2), 6.48 (d, H_5), 7.46 (d, H_6), 7.8 (m, NH), 5.3 (m, OH), 2.1 (s,CH_3); ^{13}C-NMR ($CDCl_3$, 75 MHz), 135.2 (C_1), 130.3 (C_2), 84.7 (C_3), 161.8 (C_4), 117.5 (C_5), 120.6 (C_6), 17.6 (CH_3), 168.2 (C=O); CI- EIMS : m/z [M + H^+] 278.2 [$C_8H_8INO_2$ + H]

3.5. 4-Amino-2-iodophenol (11)

An ice-cold (0-5°C) solution of diazonium chloride of 4-aminobenzenesulfonic acid (obtained from 0.393 g of 4-aminobenzene sulfonic acid) was coupled with 2-iodo phenol (**9**) (0.5 g, 2.272 mmol) in sodium hydroxide solution (1.7 ml, 2M). The reaction mixture was then stirred at this temperature for 15 minutes. The diazonium result from the latter chemical reaction was reduced *in situ* in the same reaction flask by addition of sodium dithionite solution (1.07 g, 6.145 mmol in 3 ml of water) under heating at 60 °C for 30 minutes and then stirring was continued for overnight at room temperature. After dilution with 100 ml of water, the resulting reaction mixture was extracted two times with 75 ml of ethyl acetate. The organic phases were combined and washed with brine, dried over sodium sulfate, filtered and the filtrate was evaporated under reduced pressure. The residue obtained was purified by silica gel column chromatography using dichloromethane as an eluent to give brown crystals of compound **11** as brown solid, m.p. 40 °C, yield 0.3 g (56%).
IR(cm^{-1}) : 3300 (NH), 3400 (NH); ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ ppm = 7.1 (s, H3), 6.7 (d, H5), 6.58 (d, H6), 4.3 (s, NH_2), 5.1 (s, OH); ^{13}C-NMR ($CDCl_3$, 75 MHz), δppm = 142.6 (C_1), 126.5 (C_2), 88.3 (C_3), 147.1 (C_4), 118.3 (C_5), 116.6 (C_6) CI- EIMS : m/z [M + H^+] 236 [C_6H_6INO + H].

3.6. 4-Acetamido-2-iodo phenol (12)

A mixture of acetic anhydride (880 µl, 0.131 mmol), anhydrous dichloromethane (1 ml), triethylamine (73 µl, 0.525 mmol) and a 50% solution of pentaphosphoric acid anhydride in ethyl acetate (109 µl, 0.196 mmol) was stirred for 30 minutes, then 4-amino-3-iodophenol (0.061 g, 0.262 mmol) was added. The resulting reaction mixture was stirred at room temperature for overnight. After extraction with 10 ml of ethyl acetate, the organic phase was separated, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (80: 20) as an eluent to give brown oil, yield 0.036 g (50%).
IR (cm^{-1}): 3300 (NH), 1700 (C=O); ^{1}H. NMR ($CDCl_3$, 300 MHz) : δ ppm = 7.07 (s, H_3), 6.71 (d, H_5), 7.24 (d, H6) NH (m, 7.9), OH (m, 5.1), 2.01(s, CH_3); ^{13}C.NMR ($CDCl_3$, 75 MHz), 142.4 (C_1), 90.5 (C_2), 124.9 (C_3), 161.5 (C_4), 114.7 (C_5), 123.4 (C_6), 17.7 (CH_3), 168.2 (CO); CI-EIMS : m/z [M+H^+] 278,2 [$C_8H_8INO_2$ + H].

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