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7α-FLUOROOXYCODONE

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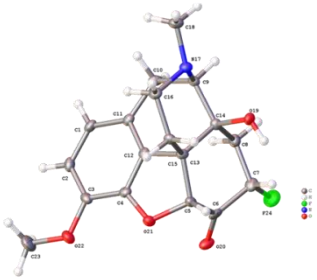


Abstract

A C(7)-fluorinated derivative of oxycodone was obtained for the first time by the electrophilic fluorination of the lithium enolate of oxycodone. The reaction involving Selectfluor proceeds stereoselectively and results in the formation of a single C(7)-epimer. The structure of the newly prepared 7*α*-fluorooxycodone was confirmed by X-ray diffraction.

Key words: opioids, oxycodone, electrophilic fluorination, morphinans.

Introduction

Oxycodone ((*5R,9R,13S,14S*)-4,5*α*-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one, **1**) [1] is one of the most widely used semisynthetic opioids in clinical practice; it amounts to the drugs that relieve pain syndrome. Along with morphine, it is usually used in the treatment of acute postoperative pain. Being an agonist of *κ*-opioid receptors and featuring lower affinity for *μ*- and *δ*-opioid receptors, oxycodone exhibits an analgesic effect comparable to that of morphine, but unlike the latter, it has increased bioavailability and half-life (3-5 h) and thus a longer analgesic action [2]. In addition to some advantage in analgesic effect in the treatment of pain in cancer patients [3], oxycodone also has a lower immunosuppressive effect compared to other opioids, in particular, relative to morphine in patients with colorectal cancer [4].

Oxycodone (**1**) was first synthesized in 1916 [5] by German scientists as a result of attempts to improve the pharmacological profile of opioids existing at that time, in particular, with the aim of reducing the level of respiratory depression from morphine and diamorphine (heroin). Oxycodone is a dihydrogenated derivative of 14-hydroxycodeinone (**3**), an oxidation product of the alkaloid thebaine (**4**), which is the main alkaloid of *Papaver Bracteatum* (Fig. 1).

Attempts to find new opioids with valuable pharmacological profiles are still ongoing. One of the main research objects are the derivatives of 14-hydroxycodeinone (**3**), which are obtained by the modification of natural structures. Majority of the most successful modifications from the pharmacological viewpoint affect the *C* ring of the morphinan backbone (highlighted in bold in structure **4** in Fig. 1) [6].

It is known that the introduction of fluorine atoms into the molecules of physiologically active compounds can significantly affect their pharmacological profile, in particular, by increasing lipophilicity, conformational changes, and increasing the stability of the molecule to metabolic processes in the human body [7]. Currently, approximately 20% of the used drugs are

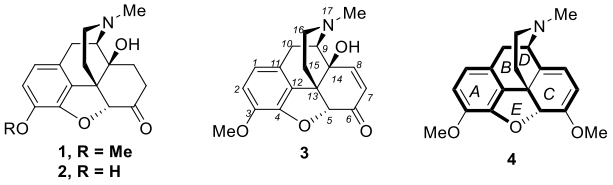


Figure 1. Alkaloid thebaine (**4**) and its derivatives: 14-hydroxycodeinone (**3**), oxycodone (**1**), oxymorphone (**2**).

fluorine-containing structures, and according to forecasts, their number will increase with the methodology development in the field of organofluorine chemistry [8].

Earlier we have successfully developed the methods for introducing different numbers of fluorine atoms into the tertiary alcohol moiety in the *C* ring of 6,14-ethenoisomorphinan derivatives [9]. The works on the development of methods for introducing fluorine atoms into the morphinan framework itself, including the 14-hydroxycodeinone derivatives, are rare and unsystematic [10]. Only one attempt to introduce a fluorine atom chemo- and stereoselectively at the C(7)-position of a codeine derivative upon opening of 6,7*α*-epoxy derivative was reported to date [11]. However, the details of the synthesis of such a 7*β*-fluorinated derivative were not disclosed.

It is known that in the liver, oxycodone is metabolized primarily to an active metabolite oxymorphone (**2**, Fig. 1), and then the C(6)-keto group can be reduced to various isomers of oxycodol and oxymorphol [12]. The presence of a strong acceptor substituent in close proximity to the C(6)-keto group could greatly affect the metabolic processes occurring with its participation, in particular, accelerate its reduction to an alcohol group, and probably increase the selectivity of the process. Therefore, the introduction of fluorine atoms in close proximity to it, namely, at the C(7) position of oxycodone, seems to be interesting and promising. The direct fluorination using numerous electrophilic fluorinating agents is widely used [13], and the application of enolates or ethers as substrates has long

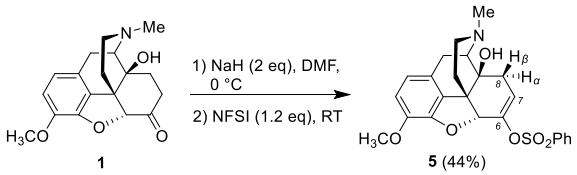
been practiced, including stereoselective modifications [14].

Herein, we report on the fluorination of alkali metal enolates obtained directly from oxycodone (**1**) using different types of electrophilic fluorinating agents (NFSI or Selectfluor), which resulted in the first example of the synthesis and characterization of the 7*α*-epimer of fluorinated oxycodone (**6**).

Results and discussion

In this work, we explored the possibility of introducing a fluorine atom at the C(7) position of oxycodone (**1**) by treating alkali metal enolates obtained directly from **1**, *i.e.*, without preliminary protection of the 14-hydroxy group, with electrophilic fluorinating agents.

The reaction of the sodium enolate of oxycodone with *N*-fluorobenzenesulfonimide (NFSI), instead of any fluorinated derivative, afforded phenylsulfonate **5** (44%) as the only reaction product (Scheme 1). Its structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy, including ^{1}H–^{1}H COSY NMR spectrum, and high-resolution mass spectrometry.

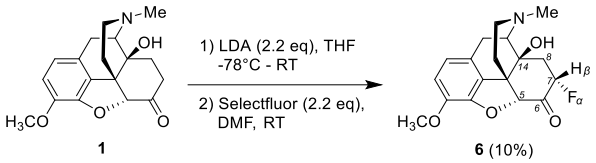


Scheme 1. Synthesis of phenylsulfonate **5**.

The lack of the carbonyl group resonance in the ^{13}C NMR spectrum of product **5** indicated that this moiety in compound **1** was transformed into an enolic hydroxy group during the reaction. The presence of a dd signal for H-7 proton in the region characteristic of olefins with spin-spin coupling constants J = 3.7 and 5.1 Hz in the ^{1}H NMR spectrum, also revealing a cross peak with both signals for H-8*α* and H-8*β* in the ^{1}H–^{1}H COSY NMR spectrum, indicates the presence of a double bond just between the C6 and C7 carbon atoms.

An analogous experiment with the sodium enolate of oxycodone using Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) as a fluorinating agent did not give a satisfactory result: the conversion of the starting oxycodone (**1**) was very low, the reaction products, as was judged from the ^{19}F NMR spectroscopic data, represented several fluorinated derivatives of the morphinane structure in trace amounts.

The fluorination of oxycodone enolate after the deprotonation of **1** with lithium diisopropylamide (LDA) under the action of Selectfluor proceeded with the low conversion (no more than 30% according to the results of several repeated experiments), but was quite selective. 7*α*-Fluorinated product **6** was isolated with 10% yield as a single isomer (Scheme 2). The second possible epimer (7*β*-fluorooxycodone) was not detected in the reaction mixture. The time and temperature of the fluorination of the oxycodone enolate appeared to insignificantly affect the yield of product **6**. Due of the high selectivity of the reaction, this result should be considered as promising for further development; however, it requires optimization of the synthesis conditions in order to increase the yield of the main reaction product.



Scheme 2. Synthesis of *α*-fluorooxycodone.

The structure of ketone **6** was confirmed by ^{1}H, ^{19}F NMR spectroscopy, high-resolution mass spectrometry, and X-ray diffraction (Fig. 2).

It should be noted that the introduction of a fluorine atom at the C(7) position of the oxycodone molecule (**1**) led to the splitting of the H-7 proton signals in the ^{1}H NMR spectra of structure **6** due to $J_{H,F}$, as well as the C-7, C-8, C-6, C-5, and C-14 carbon resonances in the ^{13}C NMR spectrum due to $J_{C,F}$.

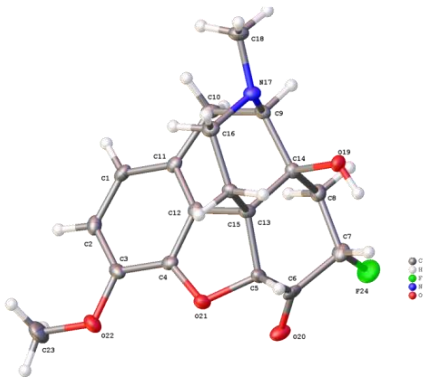


Figure 2. Molecular structure of **6**. Single crystals were obtained from a chloroform solution.

Fluorinated ketone **6** is stable both in solution during long-term storage and in the solid state, and does not epimerize upon isolation using chromatography.

An attempt to obtain 7*β*-methyl and 7*β*-phenyl derivatives of hydrocodone was reported earlier. However, they were found to rapidly epimerize to the thermodynamically more stable 7*α*-methyl- and 7*α*-phenylhydrocodone, respectively, presumably due to easy protonation from the sterically less hindered *α*-side [11, 15]. In our case, the second epimer, namely 7*β*-fluorooxycodone, if formed in some amount during the reaction, is also likely to rapidly epimerize to more stable 7*α*-epimer **6** and was not detected among the reaction products.

The reaction of the lithium enolate of ketone **1** with NFSI proceeds with a higher conversion (up to 50%), but affords, along with target product **6** (yield 12%), phenylsulfonate **5**, which was isolated in 15% yield.

Experimental section

All reactions were carried out under an argon atmosphere. All reagents were obtained from commercially available sources (ABCR, Sigma-Aldrich, Macklin) and were used without further purification. The NMR spectra (^{1}H, ^{13}C, ^{19}F) were recorded on Bruker Avance™ 300, Bruker Avance™ 400, and Bruker Avance™ 500 spectrometers in $CDCl_3$. The chemical shifts are given relative to the residual signal of $CDCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). The ^{19}F chemical shifts were measured relative to $CFCl_3$ as an external standard. The signal assignment

in the ^{1}H and ^{13}C NMR spectra was performed in some cases using 2D COSY, HMQC, and HMBC experiments. The high-resolution mass spectra (HRMS) were recorded on a Bruker maXis instrument using electrospray ionization. The melting points were measured on an Electrothermal 1002 MELTEMP® apparatus in a capillary. TLC was carried out using aluminum TLC plates with silica gel 60 F254 (Merck®) with the development with a UV lamp or in iodine vapors.

The X-ray diffraction data for **6** were collected at 120 K on a Bruker SMART APEX CCD area detector diffractometer. Using Olex2 [16], the structure was solved with the SHELXT [17] structure solution program using Intrinsic Phasing and refined with the XL [18] refinement package using Least Squares minimisation. The crystal data and structure refinement parameters are given in Table S1 in the Electronic supplementary information (ESI). CCDC 2405080 contains the supplementary crystallographic information for this paper.

***(5R,9R,13S,14S)*-6,7-Didehydro-4,5*α*-epoxy-14-hydroxy-3-methoxy-17-methyl-6-(phenylsulfonyloxy)morphinan (5).** A DMF-washed suspension of NaH (0.38 g, 9.50 mmol) in 5 mL of DMF was added to a solution of **1** (1.00 g, 3.17 mmol) in 15 mL of DMF at 0 °C upon stirring, and the resulting reaction mixture was stirred at this temperature for 0.5 h. Then NFSI (2.50 g, 7.94 mmol) was added to the resulting mixture, and the reaction mixture was gradually warmed to room temperature and left for 1 day. The mixture obtained was poured into water, and the products were extracted with chloroform (2×50 mL). The resulting organic layer was washed with water (3×70 mL), dried over Na_2SO_4, and the solvent was removed under vacuum. The residue obtained was purified by column chromatography (silica gel, $CHCl_3$–MeOH–NH_3 (aq.) = 1600:15:1) to give compound **5** (0.64 g, 44%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 2H, Ph), 7.66 (m, 1H, Ph), 7.55 (m, 2H, Ph), 6.60 + 6.69 (AB-system, J_{AB} = 8.2 Hz, 2H, H-1 + H-2), 5.62 (dd, J = 3.7, 5.1 Hz, 1H, H-7), 4.64 (br. s, 1H, OH), 4.60 (s, 1H, H-5), 3.84 (s, 3H, OCH_3), 3.14 (d, J = 18.5 Hz, 1H, H-10*β*), 2.81 (d, J = 6.4 Hz, 1H, H-9), 2.58 (dd, J = 6.4, 18.5 Hz, 1H, H-10*α*), 2.34–2.42 (m, 1H, H-16), 2.36 (c, 3H, NCH_3), 2.05–2.27 (m, 4H, H-16, H-15, 2H-8), 1.50 (m, 1H, H-15) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4, 143.6, 143.5, 136.0, 133.9, 130.5, 129.00, 128.6, 125.4, 120.7, 118.9, 114.4, 86.4, 70.3, 63.8, 56.7, 46.9, 44.7, 42.9, 31.8, 30.9, 22.0 ppm. HRMS (ESI) calcd for $C_{24}H_{25}NO_6S$ $[M + H]^+$: 456.1481, found: 456.1474.

***(5R,7S,9R,13S,14S)*-4,5*α*-Epoxy-7-fluoro-14-hydroxy-3-methoxy-17-methylmorphinan-6-one (7*α*-fluorooxycodone, 6).** A solution of LDA (3.5 mL, 2 M solution in THF) was added dropwise to a solution of **1** (1.00 g, 3.17 mmol) in 25 mL of abs. THF upon cooling to –78 °C and stirring. In 0.5 h, the reaction mixture was warmed to room temperature, Selectfluor (2.5 g, 7.06 mmol) and then 5 mL of DMF were added upon stirring, and the resulting mixture was left at this temperature overnight. Water (10 mL) was added to the reaction mixture, the pH of the aqueous layer was adjusted to alkaline reaction with ammonia solution (25% aq.). The products were extracted with chloroform (3×30 mL), the combined extracts were washed with water and dried over Na_2SO_4, the solvent was removed. The residue obtained was purified by column chromatography (silica gel, $CHCl_3$–MeOH–NH_3 (aq.) = 3200:15:1) to give compound **6** (0.11 g, 10%) as a colorless solid. Mp: 195 °C (dec.). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 + 6.65 (AB-system, J = 8.2 Hz, 2H, H-1 +H-2), 5.57 (ddd, J = 47.9, 13.0, 5.8 Hz, 1H, H-7), 5.11 (br s, OH), 4.81 (s, 1H, H-5), 3.91 (s, 3H, OCH_3), 3.17 (d, J = 18.6 Hz, 1H, H-10*β*), 2.92 (d, J = 5.8 Hz, 1H, H-9), 2.56 (dd, J = 18.6, 5.8 Hz, 1H, H-10*α*), 2.46 (dd, J = 11.9, 5.1 Hz, 1H, H-16), 2.41 (s, 3H, NCH_3), 2.37 (dd, J = 12.5, 5.1 Hz, 1H, H-15), 2.28–2.34 (m, 1H, H-8), 2.15 (td, J = 11.9, 3.8 Hz, 1H, H-16), 1.84 (ddd, J = 12.6, 6.2 Hz, 1H, H-8), 1.58 (dd, J = 12.7, 3.1 Hz, 1H, H-15) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 202.9 (d, $^{2}J_{C,F}$ =13.1 Hz, C=O), 144.8, 143.3, 128.6, 124.5, 119.9, 115.5, 90.5 (d, $^{3}J_{C,F}$ = 1.1 Hz, C(5)-C-CHF), 89.1 (d, $^{1}J_{C,F}$ = 192.8 Hz, C(7)HF), 70.00 (d, $^{3}J_{C,F}$ = 12.3 Hz, C(14)-C-CHF), 64.3, 56.9, 50.8, 45.0, 42.7, 38.0 (d, $^{2}J_{C,F}$ = 19.1 Hz, C(8)-CHF), 30.2, 21.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ –198.50 (s, 1F) ppm. HRMS (ESI) calcd for $C_{18}H_{20}FNO_4$ $[M + H]^+$: 334.1455, found: 334.1451.

Conclusions

The fluorination of the lithium enolate of oxycodone using electrophilic fluorinating agents occurs selectively with the formation of 7*α*-fluorooxycodone (**6**). It should be underscored that the transformation described in this work was carried out without preliminary protection of the C(14)-hydroxy group, since further removal of this group under certain conditions at the last stage could lead to the loss or substitution of the newly introduced target function. It is important to note the stability of resulting *α*-fluorinated ketone **6** to epimerization. Despite the rather low reaction yield, 7*α*-fluorooxycodone (**6**) itself is a promising candidate for studying the effect of replacing a hydrogen atom for fluorine on the biological activity of oxycodone. In addition, it can be an important link in the series for studying the structure–activity relationships of fluorinated derivatives of 14-hydroxycodeinone in the case of developing methods for its modification that will allow one to retain fluorine at this position, which is the goal of our further studies.

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Electronic supplementary information

Electronic supplementary information (ESI) available online: the NMR spectra of compounds **5** and **6**, the crystallographic data for compound **6**. For ESI, see DOI: 10.32931/io2454a.

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