Benzoate Group Migration in Mitsunobu Reaction of N^3-benzoyl-5-fluorouracil with Benzoic acid, 2-chloro-5-hydroxy-bicyclo[2.2.1]hept-7-ylmethyl Ester

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*By Mitsunobu reaction of N^3-benzoyl 5-fluorouracil with 2-chloro-5-hydroxy-bicyclo[2.2.1]hept-7-ylmethyl benzoate no nucleoside was obtained. Instead nucleoside we observed a benzoate group migration with the formation of bis-benzoylated compound (**5**). The structure of this compound was proved by MS, IR, ^{1}H- and ^{13}C-NMR (with complementary COSY and HETCOR spectra), and also by synthesis of the compound by benzoylation of the starting intermediate (**1**).*

Keywords: Mitsunobu synthesis, N^3-benzoyl 5-fluorouracil, 2-chloro-5-hydroxy-bicyclo[2.2.1]hept-7-ylmethyl benzoate, bicyclo[2.2.1] heptane, benzoate group migration

In a previous paper [1] we wanted to obtain a carbocyclic 5-fluorouracil nucleoside (**2**) in which the sugar moiety is replaced by a 5-Chloro-7-hydroxymethyl-bicyclo[2.2.1] hept-2-yl fragment, but instead a C^5-N^1-nucleoside resulted an O^2,O^4-compound (**3**) as major product and a N^1,O^2-compound (**4**) as minor product, with two bicyclic fragments linked to 5-fluorouracil by the two oxigens, respectively by N^1-nitrogen and O^4-oxygen atoms of the pyrimidine ring (scheme 1).

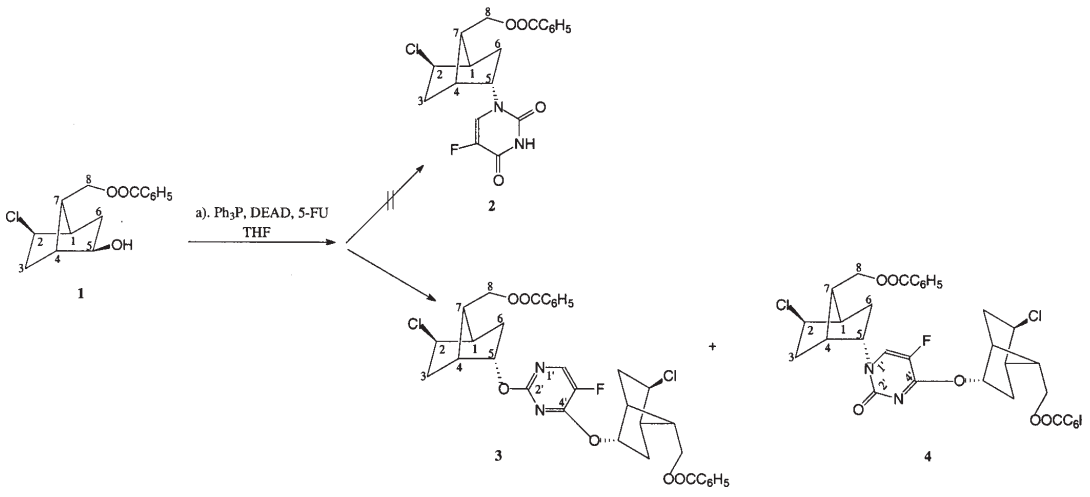
To hinder the formation of O^2-linked pyrimidine compound, we try to use in Mitsunobu reaction [2] N^3-benzoyl 5-fluorouracil, obtained by literature method [3], but no nucleoside was formed and the migration of benzoyl group was observed.

Experimental part

Progress of the reaction was monitored by TLC on Merck silica gel 60 or 60F_{254} plates (Merck) eluted with the solvent system: 1). hexane-ethyl acetate-acetic acid, 5:2:0.1, twice eluted, 2). Ethyl acetate-hexane-acetic acid, 5:4:0.1 and 3). dichlorometane-methanol, 9:1. Spots were developed to an UV lamp or with sulfuric acid (15% in etanol) or phosphomolybdic acid (5% in etanol). IR spectra were recorded on a FT-IR- 100 Perkin Elmer spectrometer and frequences are expressed in cm^{-1}, with the following abreviations: w weak, m medium, s strong, v very, br broad. MS spectra were recorded on 1200 L/MS/MS triple-quadrupole Varian with ESI interface, ^{1}H-NMR and ^{13}C-NMR spectra are recorded on Varian Gemini 300 BB and INOVA-400 spectrometers (300 and 400 MHz for ^{1}H and 75 and/or 100 MHz for ^{13}C), chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: COSY, HETCOR were done for correct assignement of NMR signals. The numbering of the atoms in compounds is presented in Schemes. THF was anhydrized on sodium wire, the other reagents were of reagent grade.

Synthesis of N^3-benzoyl 5-fluorouracil [3]

Synthesis of N^3-benzoyl 5-fluorouracil was realized from 2.6 g (0.02 mmoles) 5-fluorouracil as mentioned in the literature [3], but the product was extracted with benzene



Scheme 1. Synthesis of O^2, O^4- and N^1, O^4-5-FU-linked compounds with 2-chloro-5-hydroxy-bicyclo[2.2.1]hept-7-ylmethyl benzoate

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(3x200 mL), organic phases washed with water (50 mL), brine (50 mL), dried (Na_2SO_4), concentrated to ~40 mL and crystallized at r.t. Resulted 1.5 g product impurified with some 5-fluorouracil. Aqueous water was extracted with 2x200 mL dichloromethane, washed with the same washing waters, concentrated to dryness and crystallized from benzene, giving another 200 mg of product. Both crops were recrystallized from extraction benzine (b.p. 65-80°C), giving 1.435 g (30.64%) pure product, R_f 0.55(dichloromethane-methanol, 9:1), m.p. 151.5-153.2°C ([3a] 165-167°C; [3b] 148-152°C, [3c] 163-165°C),

Elemental analysis for $C_{11}H_7FN_2O_3$, th. (%), C: 56.42, H: 3.01, N: 11.96, found: C: 56.47, H: 3.32, N: 12.13,

IR: 3203m, 3085m, 2918m, 2520m, 2160vs, 2029vs, 1977vs, 1764s, 1713s, 1658vs, 1596s, 1432s, 1246vs, 1215vs, 1178s, 1156s, 1079m, 967s, 852s, 781s, 752s, 679s, 628m, 604s, 597s, 539s,

^{1}H-NMR(DMSO-d6, δ ppm, J Hz): **11.57**(d, NH, 5.8); **8.10-8.04**(m, 2H, H-*o*); **8.05**(d, 1H, H-6, 5.8); **7.80**(tt, 1H, H-*p*, 1.4, 7.4); **7.41**(tt, 2H, H-*m*, 1.4, 7.4), ^{13}C-NMR(DMSO-d6, δ ppm): **168.70**(COO), **156.77**(d, C-4, 27.5), **148.66**(C-2), **139.56**(d, C-5, 229.0), **135.74**(C-*p*), **130.94**(q), **130.59**(C-*o*), **129.58**(C-*m*), **127.62**(d, C-6, 32.1).

Mitsunobu reaction of N^3-benzoyl 5-fluorouracil with benzoic acid, 2-chloro-5-hydroxy-bicyclo [2.2.1]hept-7-ylmethyl (1)

To 864 mg (3 mmoles) intermediate (**1**), 705 mg (3 mmoles) N^3-benzoyl 5-fluorouracil and 787 mg (3 mmoles) triphenylphosphine in 26 mL anh. THF, cooled on an ice-water bath, 2.1 mL (3 mmoles) 40% DEAD solution in toluene were dropwise added under magnetic stirring in anh. argon atmosphere in 45 min. After 20 min., the cooling bath was removed and stirring was continued at room temperature for 3 h, then for 6 days at 62-65°C, monitoring the disappearance of the starting alcohol by tlc. It was formed a compound with R_f 0.82 (starting compound had R_f 0.32) in the solvent system 1). and R_f 0.85 in the solvent system 3). The reaction mixture was concentrated to dryness, the residue was taken-up in dichloromethane, the solution (a bit turbid) was filtered, 3 g silicagel added, concentrated and then purified by pressure chromatography (eluent: hexane-ethyl acetate, 5:2). Resulted : 507 mg (42.8%) dibenzoylated compound (**5**) as oil, analyzed by:

IR: 2972.5m, 2501w, 2159s, 2030s, 1977s, 1713vs, 1602m, 1561m, 1450s, 1407m, 1314s, 1266vs, 1176s, 1109vs, n1069s, 1025s, 955m, 906m, 710vs, 688s.

MS for $C_{22}H_{21}ClO_4$, M=384.86: (M+1): 385/387 for two Cl-isotopes, and fragments of the molecular peak: 263 and 265 (Bicyclo-monobenzoate)$^+$, 141 and 143 (bicycloalchene)$^+$, 105(C_6H_5CO)$^+$.

^{1}H-NMR-**300MHz**(CDCl$_3$, δ ppm, J Hz): **8.07**(dd, 2H, H-*o*, 1.4, 8.1); **8.00**(dd, 2H, H-*o*, 1.4, 8.1); **7.54**(tt, 2H, H-*p*, 7.6, 1.4); **7.48**(dd, 2H, H-*m*, 7.6, 8.1); **7.46**(dd, 2H, H-*m*, 7.6, 8.1); **5.21**(dddd, 1H, H-5, $^3J(H^5\text{-}H^{1'})$=1.4, $J(H^5\text{-}H^{6B})$=3.0, $J(H^5\text{-}H^{3B})$=4.4, $J(H^5\text{-}H^{6A})$=9.9); **4.81**(dd, 1H, H-8, AB syst., 9.3, 11.5); **4.61**(dd, 1H, H-8, AB syst., 6.3, 11.5); **4.10**(dd, 1H, H-2, 3.8, 7.7); **2.88**(t, 1H, H-4, 4.1); **2.79**(dd, 1H, H-3A, AB syst., $J(H^{3A}\text{-}H^2)$=8.5, $J(H^{3A}\text{-}H^{3B})$=14.7); **2.62**(d, 1H, H-1, 5.0); **2.37**(m, 1H, H-6A, $J(H^{6A}\text{-}H^{1'})$=5.0, $J(H^{6A}\text{-}H^5)$=9.9, $J(H^{6A}\text{-}H^{6B})$=14.3); **2.32**(m, 1H, H-7), **2.21**(dt, 1H, H-3B, AB syst., $J(H^{3B}\text{-}H^2)$= $J(H^{3B}\text{-}H^4)$= 4.3, $J(H^{3B}\text{-}H^{3B})$= 14.7); **1.25**(dd, 1H, H-6B, AB syst., $J(H^{6B}\text{-}H^5)$=3.0, $J(H^{6B}\text{-}H^{6A})$=14.3).

^{13}C-NMR(CDCl$_3$, δ ppm): **166.51; 166.18**(2COO); **133.29; 133.10**(2C-*p*); **130.31; 130.04**(2C$_q$); **129.74; 129.59**(2C-*o*); **128.57; 128.49**(2C-*m*), **73.17**(C-5), **62.65**(C-8); **59.73**(CH-Cl), **48.04**(C-7), **47.88**(C-1), **43.53**(C-4), **37.47**(C-6), **33.66**(C-3).

From the column, 350mg of starting compound (1) were eluted, with the same characteristics with those presented in a previous paper [1].

MS for $C_{15}H_{17}ClO_3$, M=280.75: (M+1): 281/283 for two Cl-isotopes, and fragments of the molecular peak: 263/265 (M-H_2O)$^+$, 159 and 161 (Hydroxybicyclo)$^+$, 141 and 143 (bicycloalchene)$^+$, 123(Hydroxybicyclo-HCl)$^+$, 105(C_6H_5CO)$^+$.

^{1}H-NMR(CDCl$_3$, δ ppm, *J* Hz): **7.99**(dd, 2H, H-*o*, 1.4, 7.8); **7.50**(tt, 1H, H-*p*, 1.4, 7.4); **7.38**(dd, 2H, H-*m*, 7.8, 7.4); **4.69**(dd, 1H, H-8, 9.1, 11.5); **4.51**(dd, 1H, H-8, 6.3, 11.5); **4.18**(dddd, 1H, H-5, $^3J(H^5\text{-}H^{1'})$=1.4, $J(H^5\text{-}H^{6B})$=3.0, $J(H^5\text{-}H^{3B})$=4.3, $J(H^5\text{-}H^{6A})$=9.8); **3.98**(ddd, 1H, H-2, 1.1, 4.9, 8.1); **2.78**(dd, 1H, H-3A, AB syst., $J(H^{3A}\text{-}H^2)$=8.1, $J(H^{3A}\text{-}H^{3B})$=14.3); **2.53**(d, 1H, H-4, 4.4); **2.48**(d, 1H, H-1, 5.0); **2.09**(m, 1H, H-7); **2.07**(ddd, 1H, H-6A, AB syst., $J(H^{6A}\text{-}H^{1'})$=5.0, $J(H^{6A}\text{-}H^5)$=9.8, $J(H^{6A}\text{-}H^{6B})$=13.7); **2.01**(dt, 1H, H-3B, AB syst., $J(H^{3B}\text{-}H^2)$= $J(H^{3B}\text{-}H^4)$= 4.3, $J(H^{3B}\text{-}H^{3B})$= 14.3); **0.88**(dd, 1H, H-6B, AB syst., $J(H^{6B}\text{-}H^5)$=3.0, $J(H^{6B}\text{-}H^{6A})$=14.3).

3.0, 13.7), ^{13}C-NMR(CDCl$_3$, δ ppm): **166.56**(COO), **132.97**(C-*p*), **130.29**(C$_q$); **129.58**(C-*o*), **128.37**(C-*m*), **70.03**(C-5), **63.07**(C-8); **60.25**(C-2), **48.37**(C-1), **48.04**(C-7), **45.40**(C-4), **39.42**(C-6), **32.53**(C-3).

*Benzoic acid, 2-chloro-5-benzoyloxy-bicyclo[2.2.1]hept-7-ylmethyl (**5**)*

5.62 g (20 mmoles) Intermediate (**1**) in 30 mL anh. toluene and 5 mL pyridine, after cooling on an ice-water bath, were benzoylated with 2.8 mL (22.5 mmoles) benzoyl chloride, added dropwise in 1.5 h. The cooling bath was removed and the mixture was stirred on the night, monitoring the reaction by tlc (system 2, $R_{f\,(1)}$ = 0.39, $R_{f\,(5)}$ = 0.62). A little unreacted (**1**) remains and another 0.2 mL benzoyl chloride was added and stirring was continued for 2 h. The mixture was poured into crushed ice under stirring, 200 mL toluene was added and after about 1h the phases were separated, organic phase washed with 2x100 mL satd. $NaHCO_3$ solution, 100 mL brine, dried (Na_2SO_4) and concentrated under vacuum. Resulted 7.80 g dibenzoate (**5**) as oil, in almost quantitative yield, $[\alpha]_D^{20}$= -25.50° (c=1% in THF), elemental analysis for $C_{22}H_{21}ClO_4$, C: 68.30, H: 5.47, found C: 68.00, H: 5.40

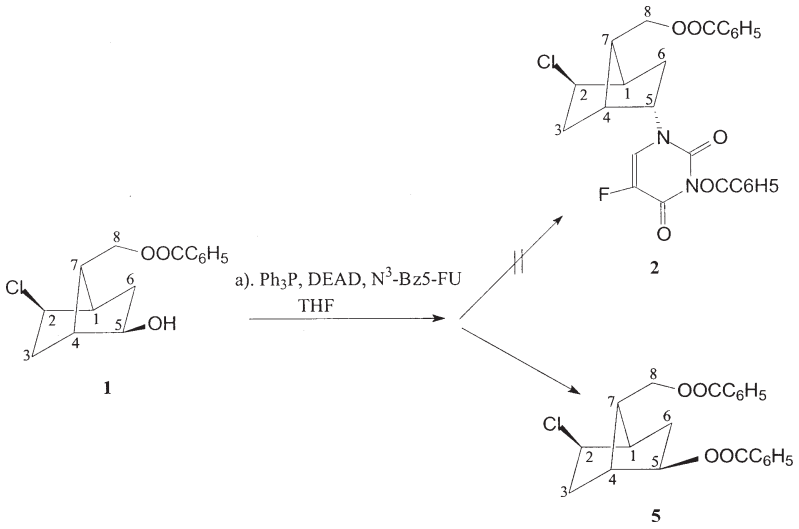
MS: (M+1): 385/387 and fragments of the molecular peak: 263 and 265 (Bicyclo-monobenzoate)$^+$, 141 and 143 (bicycloalchene)$^+$, 105(C_6H_5CO)$^+$.

^{1}H-NMR(CDCl$_3$, δ ppm, J Hz): **8.08**(d, 2H, H-*o*, 7.8, 1.4); **8.01**(d, 2H, H-*o*, 7.8, 1.4); **7.56**(tt, 2H, H-*p*, 7.8, 1.4); **7.43**(brt, 4H, H-*m*, 7.8); **5.20**(dddd, 1H, H-5, $^3J(H^5\text{-}H^{1'})$=1.4, $J(H^5\text{-}H^{6B})$=3.0, $J(H^5\text{-}H^{3B})$=4.4, $J(H^5\text{-}H^{6A})$=9.9); **4.80**(dd, 1H, H-8, AB syst., 9.2, 11.6); **4.61**(dd, 1H, H-8, AB syst., 6.2, 11.6); **4.09**(dd, 1H, H-2, 4.1, 8.1); **2.88**(t, 1H, H-4, 4.1); **2.78**(dd, 1H, H-3A, AB syst., $J(H^{3A}\text{-}H^2)$=8.1, $J(H^{3A}\text{-}H^{3B})$=14.7); **2.61**(d, 1H, H-1, 4.8); **2.37**(ddd, 1H, H-6A, AB syst., $J(H^{6A}\text{-}H^{1'})$=4.8, $J(H^{6A}\text{-}H^5)$=9.9, $J(H^{6A}\text{-}H^{6B})$=14.3); **2.34**(m, 1H, H-7); **2.20**(dt, 1H, H-3B, AB syst., $J(H^{3B}\text{-}H^2)$= $J(H^{3B}\text{-}H^4)$= 4.1, $J(H^{3B}\text{-}H^{3B})$= 14.7); **1.24**(dd, 1H, H-6B, AB syst., $J(H^{6B}\text{-}H^5)$=3.1, $J(H^{6B}\text{-}H^{6A})$=14.3).

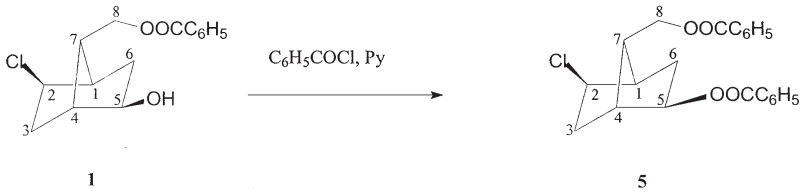
^{13}C-NMR(CDCl$_3$, δ ppm): **166.38; 166.06**(2COO), **132.98;130.54**(2C-*p*); **129.61; 129.47**(2C-*o*), **128.49; 128.37**(2C-*m*), **73.06**(C-5), **62.55**(C-8); **59.62**(CH-Cl), **47.92**(C-7), **47.77**(C-1), **43.42**(C-4), **37.34**(C-6), **33.55**(C-3).

Results and discussions

Synthesis of the nucleoside analogues, (**2**), starting from the optically active alcohol (**1**) was intended to be realized



Scheme 2. Mitsunobu reaction of N^3-benzoyl-5-fluorouracil with alcohol (**1**)



Scheme 3. Synthesis of dibenzoate (**5**) from the compound (**1**)

by Mitsunobu reaction, in the same conditions as in a previous paper [1], but replacing 5-fluorouracil with N^3-benzoyl 5-fluorouracil to hinder the formation of C^5-O^2 and O^4- bond in alkylation of 5-fluorouracil, but no compound was formed containing 5-fluorouracil moiety. Instead of wished C^5-N^1-nucleoside (**2**) it was formed the dibenzoylated compound (**5**) in 42.8% yield, which resulted from the migration of a benzoate group from N^3-benzoyl 5-fluorouracil to 5β-OH group during Mitsunobu reaction (scheme 2). No diol was observed which could result from the deprotection of the starting alcohol. Only starting alcohol (**1**) was detected.

Benzyl [4] group migration and rearrangement [5] was observed in the literature in the Mitsunobu reaction.

The structure of the dibenzoate (**5**) was proved by MS and NMR analysis. In MS molecular peak for (M+1) appear at 385/387 for the two Cl-isotopes, and fragments from these molecular peaks are: 263 and 265 (Bicyclo-monobenzoate)$^+$, 141 and 143 (bicycloalchene)$^+$, fragments with one chloro atom, and 105(C_6H_5CO)$^+$.

In ^{1}H- and ^{13}C-NMR the compound presents signals for two benzoate groups in the molecule and well recognized signals for the bicyclo[2.2.1]heptane skeleton. What is interesting is that H-5 proton looks to be H-5α because it appear as a dddd multiplet (fig. 1), due to couplings with H_6, H_4 H_1 and H_7 and this means that migration of benzoate group took place with retention of configuration on C-5 carbon atom.

To prove this configuration we synthesized dibenzoate (**5**) by benzoylation of the starting alcohol (**1**) (scheme 3) and analyzed this compound by comparison with those obtained in Mitsunobu reaction.

The same MS and also the same ^{1}H- and ^{13}C-NMR spectra were obtained for synthesized dibenzoate (**5**) as for the compound resulted in Mitsunobu reaction.

In this case it is sure that the configuration of H-5 proton is H-α and so is the configuration of H-5 proton of the compound (**5**) resulted in the above Mitsunobu reaction (fig. 1). That means that the intermediate complex formed could be hindered from the *endo*-side and access to C-5 carbon atom is preferred from the *exo*-side of the skeleton.

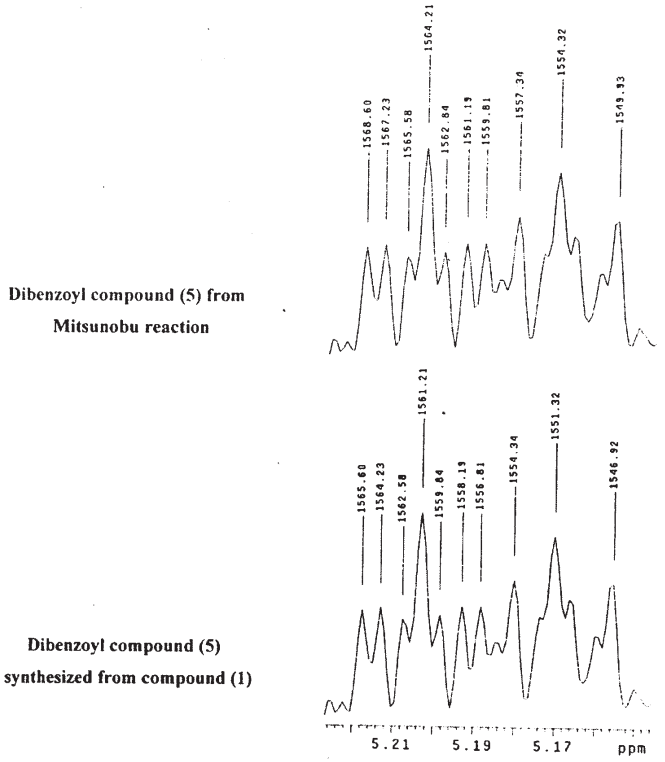


Fig. 1. ^{1}H-NMR- spectrum for H-5 proton in the compound (**5**) obtained in Mitsunobu reaction and for H-5 proton in the dibenzoyl compound (**5**) synthesized by benzoylation of the starting alcohol (**1**)

Conclusions

In the Mitsunobu reaction of N^3-benzoyl 5-fluorouracil with 2-chloro-5-hydroxy-bicyclo[2.2.1]hept-7-ylmethyl benzoate, no nucleoside was formed. Instead of wished C^5-N^1-nucleoside (**2**) dibenzoylated compound (**5**) was formed in 42.8% yield, which resulted from the migration of a benzoate group from N^3-benzoyl 5-fluorouracil to 5β-OH group during Mitsunobu reaction. Its structure was proved to be the same with that of the compound (**5**) obtained by benzoylation of the starting alcohol (**1**).

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