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THE REACTION OF POLYFLUOROKETONES WITH DIMECARBIDE – A NEW APPROACH TO 6-FLUOROALKYLMODIFICATION OF 5-HYDROXYINDOLES

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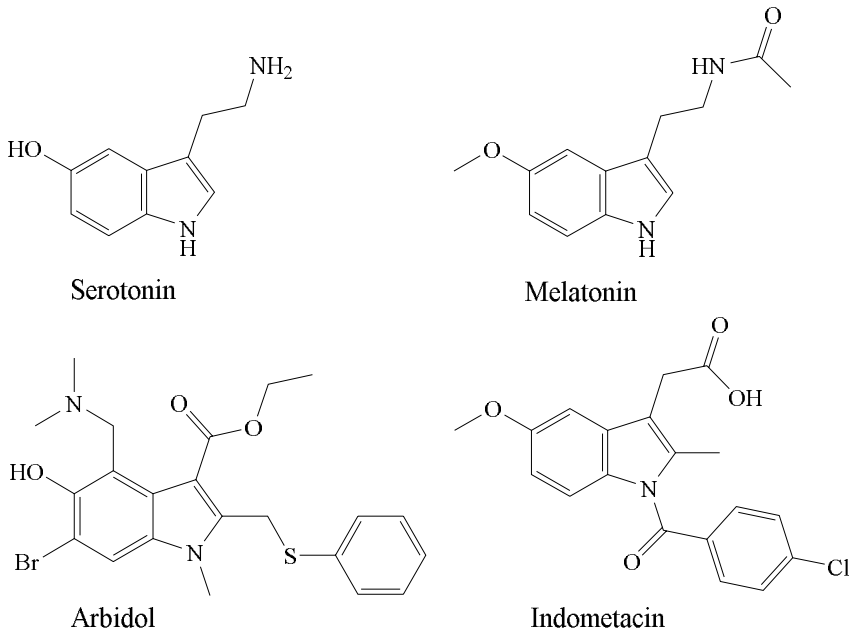
Abstract: Hexafluoroacetone **2a**, nitropentafluoroacetone **2b** and perfluorocyclohexanone **2c** are smoothly reacting with dimecarbide **1** to form products of C-6-oxyalkylation (**5a-c**) with yields of 74-90%. In the case of trifluoro- **3** and difluorochloropyruvic acid methyl esters **4**, the oxyalkylation reaction is accompanied by cyclization of the intermediate esters **6a, 7a** into the corresponding lactones **6b,7b**.

Keywords: serotonin, 5-oxyindoles, hexafluoroacetone, nitropentafluoroacetone, methyltrifluoropyruvate, methyldifluorochlorpyruvate, perfluorocyclohexanone, dimecarbine, C-oxyalkylation

5-Oxyindole derivatives (5-OI) occupy a special place in the physiology of the higher nervous system. Serotonin plays an important role of the neurotransmitter of the human CNS by regulating the transmitting pulses processes in the neurons of the cardiovascular, endocrine and other physiologists of important body systems [1, 2]. The similar to it by the structure, hormone melatonin is involved in the change control in the day and night rhythms of living organisms [3]. The synthetic derivatives of 5-OI – indomethacin and dimecarbine, for many years are used in medical practice as an anti-inflammatory and hypotensive agent, respectively [4]. The domestic Arbidol medication strongly holds the position on the market of antiviral medications [5,6].



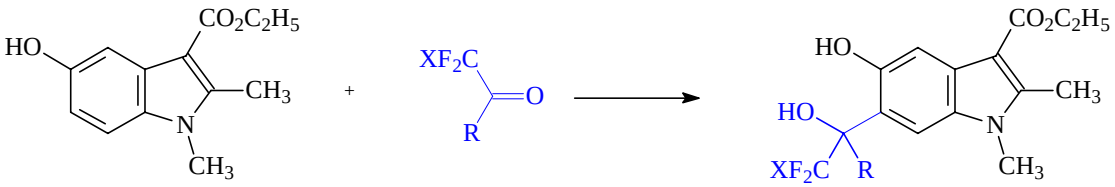
5-OI, being indoles on one side, and with the other side - phenols, have an enriched chemistry. The great contribution to its development is introduced by Grinev et al. The most typical are electrophilic substitution reactions: alkylation, acylation, halogenation, diazotization, and various aminomethylation variants [7].

It has been established that the presence of fluorine in biologically active compounds significantly affects the metabolism [8] thereof. The presence of fluorine or polyfluoroalkyl groups in the molecule increases the lipophilic property of the fluorine-containing compounds, thus making it easier to penetrate the cell protein-lipid membrane. The comparison by volume of a fluorine atom with a hydrogen atom in organic compounds, as well as by nucleophilicity with an oxygen atom, formed the basis called “the masking effect” [9]. Consequently, at present there is an increasing interest in the development of novel methods for the synthesis of fluorine-containing compounds, and more particularly to the treatment of CF_3-containing indoles, which structure is based on the compounds studied in the present work [10]. Despite the considerable success in synthetic organic chemistry, no methods of single-step introduction of fluorine-containing substituents in 5-OI in the literature are described.

Having studied the patterns of reactions of polyfluorocarbonyl compounds with phenols, naphthols, polyphenols, phenolates, 8-oxyquinolines [11], we found the convenient method of one-step fluoroalkyl modification of 5 - OI on the example of reaction of polyfluoroketones with ethyl ester of 5-oxy-1,2-dimethyl-1H-indole-3-yl carboxylic acid **1** - dimecarbine [4]. In these transformations, hexafluoroacetone **2a**, nitropentafluoroacetone **2b**, perfluorocyclohexanone **2c**, trifluoropyruvic acid methyl ester **3**, as well as the relatively recently described methyl difluorochlorpyruvate **4**, were used as electrophilic agents [12].

Heating at 120°C for 1 hour in glacial acetic acid of equimolar amounts of **1** and hexafluoroacetone has been shown to result in the formation with a high yield of the product from C-oxyalkylation of **5a** (see Scheme 1).

Scheme 1.



1 **2a-c** **5a-c**

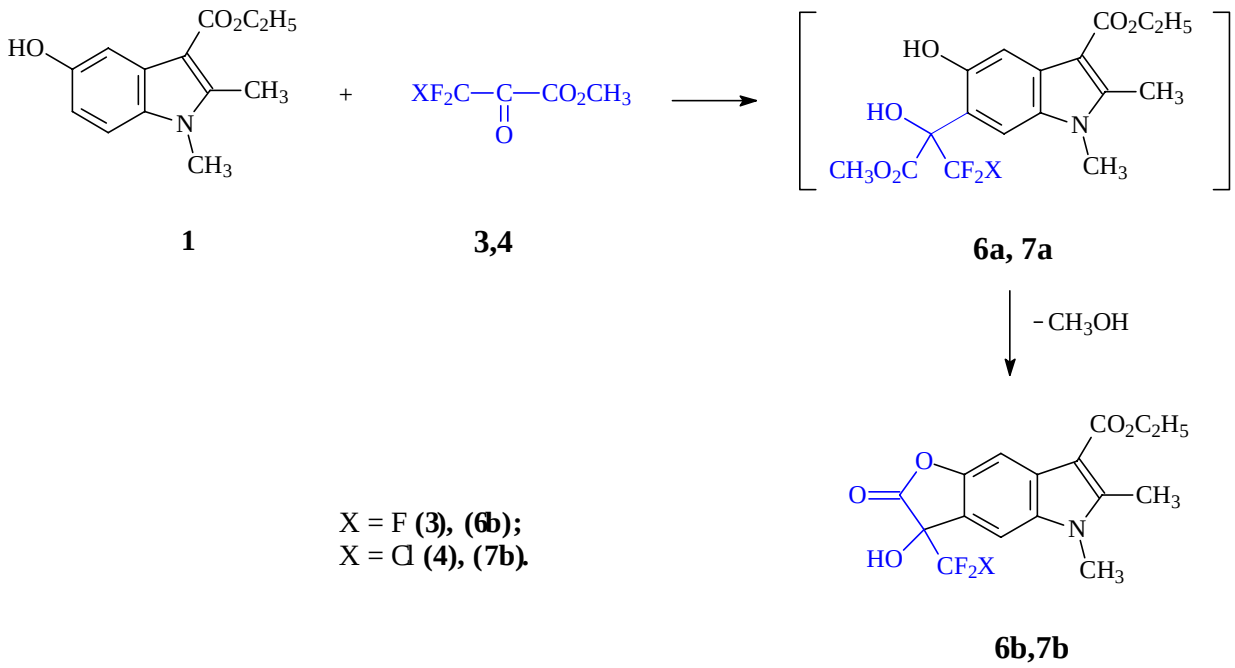
R = CF_3, X=F (2a, 5a); R = CF_3, X = NO_2 (2b, 5b); R = X = -$(CF_2)_4$- (2c,5c)

The reaction is carried out regioselectively in position 6 of oxyindole **1** with complete conversion of the latter. Under the same conditions nitropentafluoroacetone **2b** reacts with compound **1** to form product **5b** with 80% yield. Similarly, to hexafluoroacetone, the poorly studied in the oxyalkylation reactions 2,2,3,3,4,4,5,5,6,6 - dodecafluorocyclohexanone **2c** reacts with dimecarbine, forming highly fluorinated oxyindole (**5b**) with a yield of 74%.

In ^{1}H NMR spectrum of newly synthesized compounds **5a-c** significant broadening of protons signals of phenol and polyfluoropropanol OH-groups is observed. It appears that this is associated with intensive proton exchange between their oxygen atoms.

Under similar conditions, reaction is carried out with dicamcarbine with ketoesters **3** and **4** (see Scheme 2).

Scheme 2.



Under these conditions, intermediate C-6-oxyalkylation products **6a**, **7a** are cyclized to the corresponding lactones **6b**, and **7b** by yield 86.7% and 75%, respectively. It should be noted that this is the first example of using the ketoester **4** in the C-oxyalkylation reaction of similar type hetararomatic compounds.

Dimecarbine has poor solubility and acetic acid was used as a suitable high-boiling polar solvent. A relatively high reaction temperature is most necessary for better solubility of the starting 5-OI rather than for activating the reagents. It appears that C-oxyalkylation **1** can be carried out at a significantly lower temperature.

Therefore, in the example of dicamelbine it is shown that polyfluorocarbonyl compounds **2a-c** and ketoesters **3, 4** are convenient reagents for single-step addition of alpha-hydroxypolyfluoroalkyl substituent to 6 position of 5-OI, including compounds having known biological activity (antibacterial, antiviral, hypotensive, etc.).

It appears that this method of fluoroalkyl modification can be applicable to other multi-numerical Nenitzescu reaction products, including annelated oxyindoles of a more complex structure.

Presence of chelate function in the compounds **2a-c** enables obtaining different types of annelated 1,3-dioxaphosphorinanes [13], which significantly expands synthetic possibilities based on the obtained fluorine-containing oxyindoles **5a-c**.

Experimental part

^{1}H and ^{19}F NMR spectra of the obtained compounds **5a**, **5c**, **6b** and **7b** are taken in DMSO-d_6 and $CDCl_3$ on a Bruker Avance 300 device (300 and 282 MHz, respectively), compound **5b** on Bruker Avance 400 (400 and 376 MHz, respectively). Chemical shifts in ^{1}H NMR spectra are given in the

scale δ (ppm) relative to TMS (internal standard), in NMR ^{19}F spectra relative to CCl_3F (external standard). The spin-spin interaction constants are given in Hz. The elemental analysis is performed in the microanalysis laboratory of INEOS RAS. Reactions are monitored by TLC method on Merck plates (silica gel 60 F_{254}, 0.25 mm). The R_F values of the synthesized compounds are determined in the acetone-CCl_4 = 1:2 system.

5-Hydroxy-1,2-dimethyl-6-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethylethyl)-1H-indole-3-yl carboxylic acid ethyl ester (5a)

In a glass ampoule were placed 2.33 g (10 mmol) **1** and 6 ml glacial acetic acid. The ampoule is then cooled to -78°C and condensed therein 2.00 g (12 mmol) of hexafluoroacetone **2**, sealed and heated in an oil bath for 1 hour at 120°C. Ampoule is cooled to -78°C, opened, crystalline precipitate is filtered, washed with acetic acid, then benzene and dried in vacuum. Obtained: 3.60 g of compound **5a** in the form of colorless crystals, yield 90.2%, m.p. 252 -254°C (acetic acid), R_f = 0.6 (acetone-CCl_4 = 1:2).

^{1}H NMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 10,57 (br. s, 1H, OH); 8,83 (br. s, 1H, OH); 7,56 (s, 1H, Ar); 7,54 (s, 1H, Ar); 4,27 (q, 2H, O$\underline{CH_2}CH_3$, $^3J_{H\text{-}H}$=7); 3,68 (s, 3H, NCH_3), 2,70 (s, 3H, CH_3), 1,36 (t, 3H, $OCH_2\underline{CH_3}$, $^3J_{H\text{-}H}$=7).

^{19}F NMR spectrum (DMSO -d_6, δ, ppm, *J*/Hz): -73,48.

Found (%): C, 47,86; H, 3,76, N, 3,96. $C_{16}H_{15}F_6NO_4$.

Calculated (%): C, 48,13; H, 3,79, F 3,51.

6-[1-Difluoromethyl)-2,2,2-trifluoro-1-hydroxyethyl]-5-hydroxy-1,2-dimethyl-1H-indole-3-yl carboxylic acid ethyl ester (5b)

In a glass ampoule were placed 1.16 g (5 mmol) **1**, 4 ml of glacial acetic acid and 1.0 g (5.5 mmol) of nitropentafluoroacetone. The ampoule was cooled to -78°C, sealed and heated in an oil bath for 1 hour at 120°C. After cooling to -78°C, the ampoule was opened, its contents were carried out into a flask and evaporated on a rotary evaporator. Solid residue was crystallized from nitromethane. Obtained: 1.7 g of white crystalline compound **5b**. Yield is 80%, m.p. is 235°C (subl.) (nitromethane), R_f = 0.51 (acetone-CCl_4 = 1:2).

^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 10,15 (br. s, 1H, OH); 8,87 (br. s, 1H, OH); 7,13 (c, 1H, Ar); 7,43 (s, 1H, Ar); 4,37 (q, 2H, O$\underline{CH_2}CH_3$, $^3J_{H\text{-}H}$=7); 3,73 (s, 3H, NCH_3), 2,74 (s, 3H, CH_3), 1,46 (t, 3H, $OCH_2\underline{CH_3}$, $^3J_{H\text{-}H}$=7).

^{19}F NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): -73,66 (t, 3F, CF_3, $^3J_{F\text{-}F}$=5,6); -90,17 (qq, 1F, CF_2NO_2, $^2J_{F\text{-}F}$=165, $^3J_{F\text{-}F}$=7,5); -94,16 (br. qq, 1F, CF_2NO_2, $^2J_{F\text{-}F}$=165, $^3J_{F\text{-}F}$=7,5).

Found (%): C, 44,80; H, 3,64; N, 6,49. $C_{16}H_{15}F_5N_2O_6$.

Calculated (%): C, 45,08; H, 3,55; N 6,57.

6-(2,2,3,3,4,4,5,5,6,6-Decafluoro-1-hydroxycyclohexyl)-5-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid ethyl ester (5c)

In a glass ampoule were placed 1.16 g (5 mmol) of **1**, 4 ml of glacial acetic acid and 1.5 g (5.4 mmol) of perfluorocyclohexanone. Then it was cooled to -78°C, sealed and heated in an oil bath for 1 hour at 120°C. After cooling to -78°C, the ampoule was opened, its contents were evaporated on a rotary evaporator, the solid residue was crystallized from nitromethane. Obtained: 1.9 g of white crystalline compound 5c, outlet 74%, m.p. 270°C (subl.) (nitromethane), Rf = 0.56 (acetone-CCl_4= 1: 2).

^{1}H NMR spectrum (DMSO-d_6, δ, ppm, *J*/Hz): 11,51 (br. s, 1H, OH); 9,65 (br. s, 1H, OH); 7,66 (s, 1H, Ar); 7,57 (s, 1H, Ar); 4,28 (q, 2H, O$\underline{CH_2}CH_3$, $^3J_{H\text{-}H}$=7); 3,67 (s, 3H, NCH_3); 2,70 (s, 3H, CH_3); 1,36 (t, 3H, $OCH_2\underline{CH_3}$, $^3J_{H\text{-}H}$=7).

^{19}F NMR spectrum (DMSO-d_6, δ, ppm, *J*/Hz): - 34,85 (dd, 2F, CF_2, $^2J_{F\text{-}F}$=282); 38,99 (dd, 2F, CF_2, $^2J_{F\text{-}F}$=271); - 42,58 (dd, 1F, CF_2, $^2J_{F\text{-}F}$=267); - 54,44 (dd, 2F, CF_2, $^2J_{F\text{-}F}$=282); 58,28 (dd, 2F, CF_2, $^2J_{F\text{-}F}$=271); 62,50 (dd, 1F, CF_2, $^2J_{F\text{-}F}$=282).

Found (%): C, 44,51; H, 3,15, F 36,81. $C_{19}H_{15}F_{10}NO_4$.

Calculated (%): C, 44,63; H, 2,96, F 37,16.

3-Hydroxy-5,6-dimethyl-2-oxo-3-trifluoromethyl-3,5-dihydro-2H-1-oxa-5-aza-s-indacene-7-yl carboxylic acid ethyl ester (6b)

Into a glass flask equipped with a reflux condenser with a calcium chloride tube and a magnetic stirrer with heating were placed 2.33 g (10 mmol) **1**, 6 ml of glacial acetic acid, 1.8 g (12 mmol) **3** and refluxed for 1 h at 120°C. Then reaction mass was cooled to 20°C, precipitate is filtered, washed with acetic acid, then benzene and dried in vacuum. Obtained: 3.1 g of compound (**6b**) in the form of colorless crystals, yield 86.8%, R_f = 0.48 (acetone- CCl_4= 1:2), m.p. 250-252°C (ethanol).

^{1}H NMR spectrum (DMSO -d_6, δ, ppm, *J*/Hz): 8,33 (s, 1 H, OH); 7,83 (br. s, 1 H, Ar); 7,76 (s, 1 H, Ar); 4,30 (q, 2 H, O$\underline{CH_2}CH_3$, $^3J_{H\text{-}H}$ = 7,0); 3,79 (s, 3 H, N$\underline{CH_3}$); 2,74 (s, 3 H, CH_3); 1,36 (t, 3 H, $OCH_2C\underline{H_3}$, $^3J_{H\text{-}H}$ = 7,0);

^{19}F NMR spectrum (DMSO -d_6, δ, ppm): -77,5 (s, 3F, CF_3).

Found (%): C, 53,83; H, 4,08; N, 3,96. $C_{16}H_{14}F_3NO_5$.

Calculated (%): C, 53,79; H, 3,95, N 3,92.

3-(Difluoromethyl)-3-hydroxy-5,6-dimethyl-2-oxo-3-trifluoromethyl-3,5-dihydro-2H-oxa-5-aza-s-indacene-7-yl carboxylic acid ethyl ester (7b)

Into a glass flask equipped with a reflux condenser with a calcium chloride tube and a magnetic stirrer with heating were placed 1.17 g (5 mmol) **1**, 3 ml of glacial acetic acid, 1 g (5.8 mmol) **3** and refluxed for 4 hours. Then the reaction mass was evaporated on a rotary evaporator, the resulting residue was crystallized from nitromethane. Obtained: 1.4 g of white substance **7b**, 75% yield, R_f = 0.49 (acetone- CCl_4= 1:2), m.p. 247 -248°C (nitromethane).

^{1}H NMR spectrum (DMSO -d_6, δ, ppm, *J*/Hz): 8,41 (s, 1 H, OH); 7,81 (br. s, 1 H, Ar); 7,75 (s, 1 H, Ar); 4,30 (q, 2 H, $OC\underline{H_2}CH_3$, $^3J_{H\text{-}H}$ = 7,0); 3,78 (s, 3 H, $NC\underline{H_3}$); 2,74 (s, 3 H, CH_3); 1,35 (t, 3 H, $OCH_2C\underline{H_3}$, $^3J_{H\text{-}H}$=7,0);

^{19}F NMR spectrum (DMSO -d_6, δ, ppm): -66,53 (d, 1F, CF_2Cl, -65,97 (d, 1F, CF_2Cl, $^2J_{F\text{-}F}$=163,8);

Found (%): C, 51,27; H, 3,87; N, 3,88. $C_{16}H_{14}ClF_2NO_5$.

Calculated (%): C, 51,42; H 3,78; N, 3,75.

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