ON SOME PECULIARITIES OF ETHYL 5-HYDROXY-1,2-DIMETHYL-1*H*-3-INDOLECARBOXYLATE SYNTHESIS

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Abstract: The increase of yield up to 63% of ethyl 5-hydroxy-1,2-dimethyl-1*H*-3-indolecarboxylate was obtained via the interaction of *p*-benzoquinone with N-methyl-β-aminocrotone ether in mixture of glacial acetic acid/ethyl acetate.

Keywords: derivatives of 5-oxindole, cardio-vascular remedies.

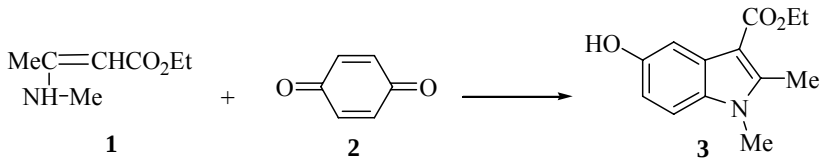
Introduction

Many physiologically active compounds with a wide spectrum of activities have been found among indole derivatives [1-5]. A representative of this series – preparation "Dimecarbine" - ethyl 5-hydroxy-1,2-dimethyl-1*H*-3-indolecarboxylate has been suggested for treatment of cardio-vascular diseases [6,7].

Results and discussion

It is well known that the chemical reaction forming 5-hydroxyindole derivatives from benzoquinone and β-aminocrotonic esters represents the classical Nenitzescu indole synthesis [8-10].

The synthesis of ethyl 5-hydroxy-1,2-dimethyl-1*H*-3-indolecarboxylate **3** consists of the cycle formation reaction between 1,4-benzoquinone **2** and ester **1** in acetone or 1,2-dichloroethane.



1 **2** **3**

However, both reported methods gave only up to 18% of targeted compound **3.** Such a low yield of the product can, probably, be explained by the instability of benzoquinone due to oxidation, which results in the breaking of the cycle or the polymer formation. Moreover, the spontaneous transformation of quinone into hydroquinone, which, in turn forms with quinone the colored quinhydrone, may influence upon the yield of the final product.

On the other side, it is known the initial interaction of the acetic acid with β-aminocrotonic esters and *p*-benzoquinones leads to the suppression of side reaction [10].

With the optimized conditions in our hands, the scope of the reaction was examined with variety of solvents. Finally, it was find that the replacement 1,2-dichloroethane or acetone by solution of the acetic acid in ethyl acetate leads to the augmentation of the yield of compound **3** up to 63%. It is worth noting that, it is possible to isolate **3** after a single recrystallization of the formed precipitate (look experimental part).

Conclusion

In summary, we have described a reaction of *p*-benzoquinone with N-methyl-β-aminocrotone ether in mixture of glacial acetic acid/ethyl acetate. This method represents a simplicity approach for preparing and isolation of the ethyl 5-hydroxy-1,2-dimethyl-1*H*-3-indolecarboxylate.

Experimental methods

All the used solvents were of reagent quality, and all commercial reagents were used without additional purification. Removal of all solvents was carried out under reduced pressure. Analytical TLC plates were Silufol® UV-254 (Silpearl on aluminium foil, Czecho-Slovakia). IR spectra were recorded on a Spectrum 100 FT-IR spectrophotometer (Perkin –Elmer) using the universal ATR sampling accessory. ^{1}H and ^{13}C NMR spectra have been recorded for $(CD_3)_2SO$ 2-% solution on a "Bruker -Avance III" (400.13 and 100.61 MHz).

Ethyl N-methyl-β-aminocrotonate 1 has been prepared according to the known procedure [7].

Preparation of ethyl 5-hydroxy-1,2-dimethyl-1*H*-3-indolecarboxylate 3. The mixture of **1** (7.9 g, 0.055 mol) and acetic acid (3.2 ml, 0.053 mol) in ethyl acetate (30 ml) were added to a solution of 5g (0.046 mol) of **2** and

glacial acetic acid (2.7 ml, 0.044 mol) in ethyl acetate (35 ml) so that the temperature in the reaction mass does not exceed 30°C (use ice/water bath). The residue was stirred for 1 hour, followed by distillation of the solvent (20 ml) and storing in the refrigerator for 24 hours at 0-10°C. The formed precipitate is separated, washed on filter by means of cold ethyl acetate. In result 7.2 g of solid substance with m.p. 180-190°C is obtained. After recrystallization from ethyl acetate 6.79 g of **3** were obtained. The yield was 63%. M.p. 215-216^{0}C. Lit. [7]. M.p. 210-215^{0}C. IR (ν/cm^{-1}): 3274 (OH), 2991, 2941, 1445, 1375 (Me, CH_2), 2791 (N-Me), 1751 (C=O), 1637, 1622, 1595, 1521, 1479, 1019, 870, 835, 803, 764, 668 (indole), 1333, 1212, 1288, 1093 (C-O). Spectrum NMR ^{1}H (δ, ppm, *J*/Hz): 1.35, t (3H, -CH_2Me, *J*=4), 2.68 s (3H, Me-C=), 3.64 s (3H, N-Me), 4.28, q (2H, -CH_2Me, *J*=4), 6.67, 6.68 d, d (1H, ^{6}CH, $J_{4,6}$=2.4, $J_{6,7}$=8.4), 7.25 d (1H, ^{7}CH, *J*=8.8), 8.47 d (1H, ^{4}CH, $J_{4,6}$=2.4), 8.95 s (1H, OH). Spectrum NMR ^{13}C (δ, ppm): 165.60 (CO_2), 153.10 (^{5}C), 145.67 (^{2}C), 131.14 (^{7a}C), 127.56 (^{3a}C), 111.72 (^{6}C), 110.69 (^{7}C), 105.95 (^{4}C), 102.37 (^{3}C), 59.06 (CH_2), 29.98 (NMe), 14.97 (^{2}CMe), 12.08 (CH_2Me). Mol. For. $C_{13}H_{15}NO_3$. Cal. C 66.94; H 6.48; N 6.0. Find C 67.3; H 6.13; N 6.28.

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