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DIASTEREOCONTROLLED SYNTHESIS OF 6-HYDROXY-1,3-DIMETHYL-5-(*R*,R**-4-PHENYL-1,2,3,4-TETRAHYDRO-1H-β-CARBOLIN-1-YL)-1H-PYRIMIDINE-2,4-DIONE

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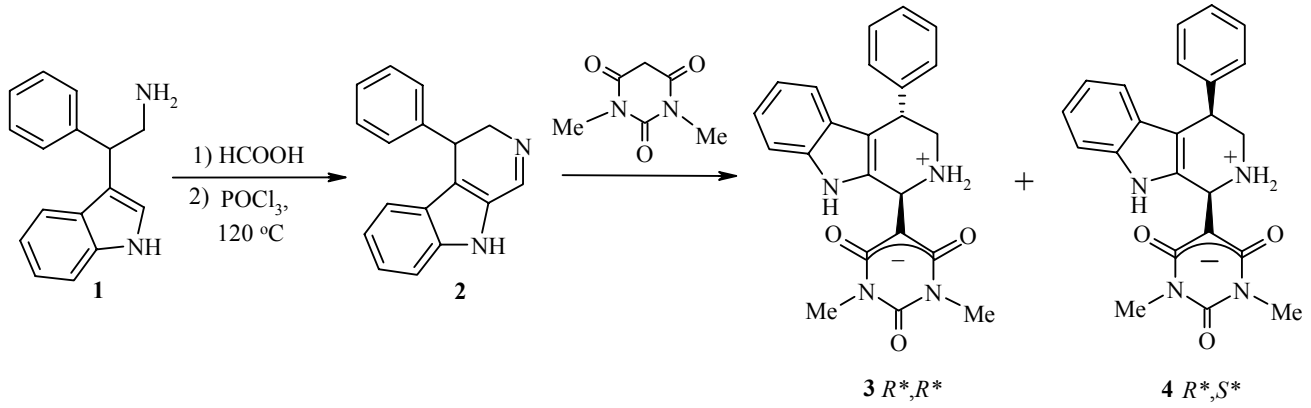
While continuing work on synthesis and study of novel β-carboline systems [1, 2], we obtained 4-phenyl-3,4-dihydro-β-carboline (**2**) (a representative of the previously undescribed group of 4-aryl-substituted 3,4-dihydro-β-carbolines) by formylation of β-phenyltryptamine (**1**) followed by cyclization under Bischler–Napieralski reaction conditions. In contrast to known derivatives of this series, which are readily formed when the corresponding N-acyltryptamines are treated with phosphorus oxychloride [3], synthesis of compound **2** required considerably more vigorous conditions and was accompanied by secondary processes; the overall yield was only 20%.

Since the diastereoselectivity is determined by either stereoelectronic factors or by steric factors [4], we hypothesized that if we used compound **2** in a Michael reaction and we used 1,3-dimethylbarbituric acid as the second component, then the reaction products would consist of two diastereomers with predominance of the *R**,*R**-isomer **3**:



This stereochemical result was also detected; the diastereoselectivity was 52%.

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Earlier we showed that in the reaction of barbituric acids with 3,4-dihydro-β-carboline, the zwitterionic 2,4,6-trioxopyrimido-1,2,3,4-tetrahydro-1H-β-carboline systems are formed. We established that addition of 1,3-dimethylbarbituric acid to **2** leads to 1,3-dimethyl-6-hydroxy-5-(4-phenyl-1,2,3,4-tetrahydro-1H-β-carbolin-1-yl)-1H-pyrimidin-2,4-dione (**3,4**), also having a zwitterionic structure.

The structure of the compounds obtained was studied using one-dimensional and two-dimensional NMR spectroscopy (Bruker DRX-500 with operating frequencies 500 MHz and 125 MHz for protons and ^{13}C nuclei respectively, TMS). In the one-dimensional ^{1}H and ^{13}C NMR spectra, we observed two sets of signals with different intensities, corresponding to the two diastereomers. The signals were assigned by analysis of the two-dimensional COSY, HSQC, and HMBC spectra. The three-dimensional structure of each diastereomer was determined using two-dimensional H–H NOE (NOESY) spectroscopy with a gradient technique, which made it possible to identify close protons.

β-Phenyltryptamine (1). A mixture of 3-(2-nitro-1-phenylethyl)indole (26.6 g, 0.1 mol) [5] in 94% alcohol (100 ml) and freshly prepared Raney nickel (1 g) was boiled for 60 h; another portion of catalyst was added any time the boiling stopped. The reaction mixture was filtered and the filtered out catalyst was washed with hot alcohol (3 × 10 ml). The filtrate was evaporated. The residue was dissolved in anhydrous ether and a saturated solution of HCl in ether was added. The hydrochloride formed was filtered out, suspended in ether, and shaken with an aqueous solution of base. The ether solution was dried with $MgSO_4$ and evaporated. Yield 21 g (90%); mp 131-132°C. According to the data in [5], mp 131-132°C (ethyl acetate).

4-Phenyl-3,4-dihydro-β-carboline Monohydrate (2). A solution of β-phenyltryptamine **1** (10 mmol) in distilled formic acid (20 ml) was heated with distillation of the solvent for 30 min, bringing the temperature of the reaction mass up to 145°C. After cooling, water (30 ml) and chloroform (20 ml) were added, the organic layer was separated and washed with water. The solvent was distilled off under vacuum and N-formyl-β-phenyltryptamine (2.40 g) was obtained as a slowly crystallizing oil. Freshly distilled phosphorus oxychloride (7 ml) was added to the compound obtained and stirred until dissolved, heated for 1.5 h with simultaneous distillation of $POCl_3$, raising the temperature of the reaction mass up to 120°C, and then the reaction mixture was held at 120-121°C for another 30 min. The mixture was cooled and poured into ice water (50 g) and after the exothermic reaction was completed, the solution was filtered and the precipitate was treated twice with 50 ml portions of 5% HCl. The combined filtrates were alkalinized with 25% ammonium hydroxide and the precipitate was filtered out and washed with water. The precipitate was dissolved in 5% HCl (10 ml), the insoluble portion was removed and the solution was alkalinized with ammonia. We obtained 0.52 g of compound **2** as the monohydrate; mp 116°C (with dehydration). Yield 22%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.87 and 4.23 (m, AB-system, 1H+1H, $\underline{CH_2}CH$); 4.39 (1H, m, CH); 6.95-7.70 (9H, m, H_{arom}); 8.69 (1H, br. s, NH); 11.37 (1H, br. s, NH).

6-Hydroxy-5-(4-phenyl-1,2,3,4-tetrahydro-1H-β-carbolin-1-yl)-1H-pyrimidine-2,4-dione (3,4). Carboline **2** (1.1 mmol) were added to a solution of 1,3-dimethylbarbituric acid (1 mmol) in hot CCl_4 (10 ml); the reaction mixture was heated for 10 min and allowed to stand for 2 h at 20°C. The precipitate was separated, washed with hot CCl_4, and dried at 40°C in a vacuum desiccator. Yield 0.29 g (74%). Light yellow crystals; mp 229°C.

Characteristic signals in the ^{1}H NMR spectrum of diastereomer **3** (DMSO-d_6), δ, ppm: 3.12 (1H, s, C$\underline{H}$, barb. acid); 5.93 (1H, s, C$\underline{H}NH_2$); 4.53 (1H, s, CHC_6H_5), 10.67 (1H, br. s, NH). Characteristic signals in the ^{1}H NMR spectrum of diastereomer **4** (DMSO-d_6), δ, ppm: 3.12 (1H, s, C$\underline{H}$, barb. acid); 5.82 (1H, s, C$\underline{H}NH_2$); 4.47 (1H, s, CHC_6H_5); 10.75 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 402 $[M]^+$ (17). Found, %: C 69.83; H 5.84; N 13.78. $C_{23}H_{22}N_4O_3$. Calculated, %: C 68.64; H 5.51; N 13.92.

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