DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 4,5,6,7-TETRAHYDROINDOLE DERIVATIVES

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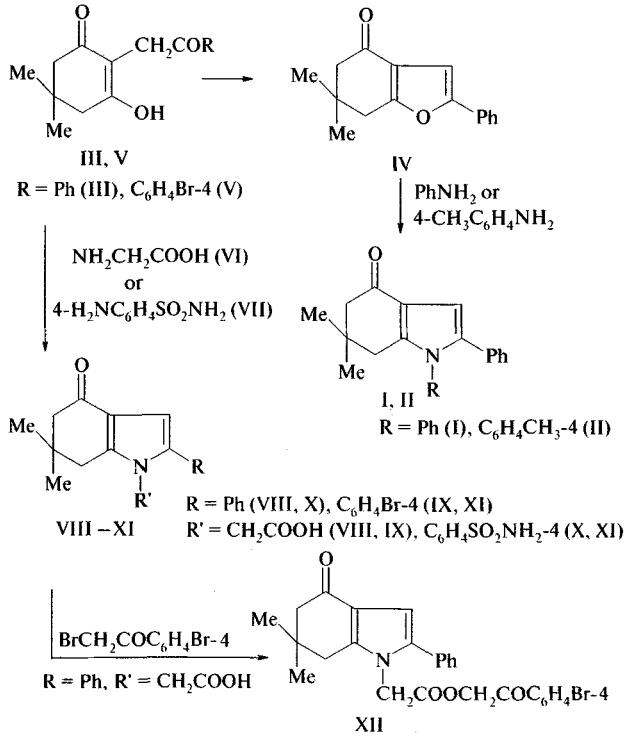
4,5,6,7-Tetraindole derivatives are used as semiproducts in the synthesis of acetylcholinesterase (ACE) inhibitors [1]. According to [2], tetraindole derivatives I and II (see the scheme below) can be synthesized by intramolecular cyclization of 2-phenacyldimedone (III) followed by amination of the intermediate 6,6-dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydrobenzofuran (IV) by aniline or 4-toluidine in AcOH.

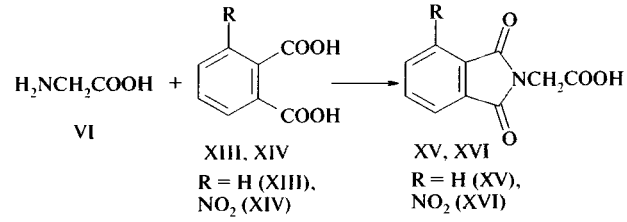


In this work, we have studied the possibility of aminating compounds III, IV, and 2-(4-bromophenacyl)dimedone (V) by bifunctional amines such as glycine (VI) and 4-aminobenzenesulfonamide (VII) in order to obtain 1-(carboxymethyl)-2-phenyl- (VIII), 2-(4-bromophenyl)-1-(carboxymethyl)- (IX), and 1-(4-sulfamoylphenyl)-2-phenyl- (X), -and 2-(4-bromophenyl)-1-(4-sulfamoylphenyl)- (XI) -6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindoles to be subsequently used for the synthesis of 1-substituted tetraindole derivatives.

After several unsuccessful attempts at accomplishing the cyclocondensation of compounds III and V with amines VI and VII in an AcOH medium, we have established that tetraindole derivatives VIII – XI can be obtained at an acceptable yield by condensation with propionic acid (PA).

Compounds VIII – XI can be isolated in the pure form by merely diluting the reaction mixtures with water, followed by reprecipitation (for VIII and IX) with hydrochloric acid from aqueous K_2CO_3 solutions or by washing the residues (for X and XI) with acetone and ethanol.

The proposed structures of tetraindole derivatives VIII – XI were confirmed by ^1H NMR spectra and by converting compound VIII into 4-bromophenacyl ester (XII) (see the experimental part below).



The catalytic activity of PA is also manifested in the reaction of amination of some dicarboxylic acids. For example, heating phthalic (XIII) or 3-nitrophthalic (XIV) acids with

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glycine (VI) in PA leads to formation of the corresponding imides (XV and XVI, respectively) at a 83 – 84% yield.

With respect to the yield of the products and simplicity of the procedure, the reaction pathway proposed for the synthesis of imides XV and XVI is competitive to the method descried previously [3].

EXPERIMENTAL PART

The ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer using samples dissolved in DMSO-d_6. The course of reactions was monitored and purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in a benzene – ethyl acetate (1 : 1) system; the spots were visualized under UV illumination. Some physicochemical characteristics of the synthesized compounds are listed in Table 1. The data of elemental analyses agree with the results of calculations according to the empirical formulas.

6,6-Dimethyl-1-(carboxymethyl)-4-oxo-2-phenyl-4,5,6,7-tetrahydroindole (VIII). A mixture of 2.6 g (10 mmole) of 2-phenacyldimedone (III) [4], 1 g (13 mmole) of glycine, and 20 ml of PA was stirred for 4 h on a bath at 185 – 195°C, cooled to ~20°C, diluted with water, and allowed to stand for 12 h. The precipitate of compound VIII was filtered, washed with water, and reprecipitated with diluted HCl from an aqueous K_2CO_3 solution. The final precipitate of VIII was again washed with water and dried at 80 – 90°C in a vacuum of 20 Torr. Yield of compound VII, 2.5 g; ^{1}H NMR spectrum (δ, ppm): 1.14 (s, 6H, $2CH_3$), 2.26 (s, 2H, CH_2), 2.65 (s, 2H, CH_2), 4.59 (s, 2H, CH_2), 6.35 (s, 1H, 3-H), 7.25 – 7.47 (m, 5H, H arom).

2-(4-Bromophenyl)-6,6-dimethyl-1-(carboxymethyl)-4-oxo-4,5,6,7-tetrahydroindole (IX). Compound IX was obtained by a procedure similar to that used for the synthesis of VIII, proceeding from glycine and 2-(4-bromophenacyl)dimedone (V) [5]. ^{1}H NMR spectrum (δ, ppm): 1.12 (s, 6H, $2CH_3$), 2.24 (s, 2H, CH_2), 2.63 (s, 2H, CH_2), 4.68 (s, 2H, CH_2), 6.37 (s, 1H, 3-H), 7.24 (d, 2H, J 8.0 Hz, H arom), 7.57 (d, 2H, J 8.0 Hz, H arom).

6,6-Dimethyl-4-oxo-1-(4-sulfamoylphenyl)-2-phenyl-4,5,6,7-tetrahydroindole (X). Compound X was obtained by a procedure similar to that used for the synthesis of VIII, proceeding from 2-phenacyldimedone and 4-aminobenzenesulfonamide. After diluting the reaction mixture with water, the precipitate of X was sequentially washed with water, aqueous K_2CO_3 solution, and acetone. ^{1}H NMR spectrum (δ, ppm): 1.11 (s, 6H, $2CH_3$), 2.30 (s, 2H, CH_2), 2.52 (s, 2H, CH_2), 6.67 (s, 1H, 3-H), 7.32 (m, 11H, NH_2 and H arom).

2-(4-Bromophenyl)-6,6-dimethyl-4-oxo-1-(4-sulfamoylphenyl)-4,5,6,7-tetrahydroindole (XI). Compound XI was obtained by a procedure similar to that used for the synthesis of VIII, proceeding from 2-(4-bromophenacyl)dimedone and 4-aminobenzenesulfonamide. After diluting the reaction mixture with water, the precipitate of XI was sequentially washed with water, acetone, and alcohol. ^{1}H NMR spectrum (δ, ppm): 1.10 (s, 6H, $2CH_3$), 2.31 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 6.65 (s, 1H, 3-H), 7.00 (d, 2H, H arom, J 8/0 Hz), 7.36, (m, 6H, NH_2 and H arom), 7.92 (d, 2H, J 8.0 Hz, H arom).

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Initial compounds: ketone or carboxylic acid	Initial compounds: amine	Yield, %	M.p., °C	Empirical formula
VIII	III	VI	83	219 – 220	$C_{18}H_{19}NO_3$
IX	V	VI	80	225 – 227	$C_{18}H_{18}BrNO_3$
X	III	VII	40	> 250	$C_{22}H_{22}N_2O_3S$
XI	V	VII	41	> 250	$C_{22}H_{21}BrN_2O_3S$
XV	XIII	VI	83	193 – 196 [3]	$C_{10}H_7NO_4$
XVI	XIV	VI	84	208 – 211 [3]	$C_{10}H_6N_2O_6$

6,6-Dimethyl-1-(carboxymethyl)-4-oxo-2-phenyl-4,5,6,7-tetrahydroindole 4-bromophenacyl ester (XII). A mixture of 0.34 g (1.14 mmole) of compound VIII, 0.27 g (0.97 mmole) of 4-bromophenacyl bromide, and 0.3 g $NaHCO_3$ in 10 ml of DMF was stirred for 24 h at ~20°C and diluted with water. The precipitate was filtered and washed with water and ether to obtain 0.45 g (94%) of compound XII; m.p., 161 – 163°C; CHBrNO; ^{1}H NMR spectrum (δ, ppm): 1.15 (s, 6H, $2CH_3$), 2.26 (s, 2H, CH_2), 2.72 (s, 2H, CH_2), 4.88 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.38 (s, 1H, 3-H), 7.44 (m, 5H, H arom), 7.74 (d, 2H, J 8.0 Hz, H arom), 7.93 (d, 2H, J 8.0 Hz, H arom).

N-Phthaloylglycine (XV). A mixture of 1 g (6 mmole) of phthalic acid and 0.5 g (6.2 mmole) glycine in 5 ml of PA was stirred for 2 h on a bath at 170 – 180°C, cooled to ~20°C, diluted with water, and allowed to stand for 12 h at 20°C. Then the precipitate was filtered, washed with water, and dried to obtain 1 g of imide XV.

N-(3-Nitrophthaloyl)glycine (XVI). Compound XVI was obtained by a procedure similar to that used for the synthesis of imide XV, proceeding from 3-nitrophthalic acid ad glycine.

The resulting imides XV and XVI show no depression in the melting temperature when mixed with known samples of these compounds and exhibit the same R_f values.

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