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Reactions of 3,4-Dimethoxyphenylethylaminomethylidene Derivatives of Tri-, Tetramethylene-4-Quinazolones and Formaldehyde

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Abstract

The reaction of 3-(3,4-dimethoxyphenylethyl)aminomethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one **3a**, 4-(3,4-dimethoxyphenylethyl)amino)-methylidene-1,2,3,4-tetrahydropyrido[2,1-b]-quinazoline-10-one **3b** and formaldehyde in acid medium was studied. Instead of the expected Mannich products, bis-derivatives that are deoxyvasicinone and homoveratryl amine were obtained from **3a**, and mackinazolinone – from **3b**. The structure of the synthesized compounds was confirmed by data from IR, NMR and mass spectroscopy.

Key words: desoxyvasicinone, mackinazolinone, 3-(3,4-dimethoxyphenylethyl)aminomethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one, 4-(3,4-dimethoxyphenylethyl)amino)-methylidene-1,2,3,4-tetrahydropyrido[2,1-b]-quinazoline-10-one

INTRODUCTION

Tricyclic quinazoline alkaloids are found in plants of the species *Peganum*, *Adhatoda*, *Galega*, *Galium*, *Nitraria*, *etc*.[1]. Alongside with monomer bases, dimer alkaloids that are dipegine and dipeginol containing the remnants of desoxyvasicine and desoxypéganine species have been found in the plant *Peganum harmala* [2]. Tricyclic quinazoline derivatives entered medical practices as pharmacologically active compounds (*e. g.* desoxypéganine is an antiangiogenic agent also called desoxypéganine hydrochloride) [3, 4].

The presence in a molecule of quinazoline alkaloids of several reaction centres able to enter into electrophilic substitution or addition reactions, as well as simplicity of methods for their preparation [5–10] make these compounds attractive synthones for further syntheses [11].

In our previous report [12], we demonstrated that 3-hydroxymethylidene-1,2,3,9-tetrahydro-pyrrolo[2,1-b]-quinazoline-9-one obtained from desoxyvasicinone **2a** in the enol form [11, 13] reacted with both primary and secondary amines with the formation of α-aminomethylmethylidene quinazolines in high yields, while the formyl derivative of mackinazolinone **2b** existing in the aldehyde form interacted with primary amines only [14].

An opportunity for cyclization of compounds **3a,b** in trifluoroacetic acid medium was studied. In this case, the process was completed by the formation of desoxyvasicinone **2a** or mackinazolinone **2b** and 3,4-dihydroisoquinoline **1,** correspondingly, by elimination of the aminomethylidene fragment (or methyl-ideneiminium trifluoroacetate salt) from position 3 (or 4). The latter was cyclised to 6,7-dimethoxy-3,4-dihydroisoquinoline **1** [15, 16].

The present work continues to study cyclization of compounds **3a,b**, using Mannich reaction conditions (boiling with 30 % formalin in methanol acid media) with the purpose of obtaining dimer compounds consisting of quinazoline and isoquinoline units.

RESULTS AND DISCUSSION

Mannich cyclization turned out to be an unacceptable method for synthesis of the target bis-derivatives, despite a relatively high reactivity of the H-6′ atom that was efficiently used in synthesis of tetrahydroisoquinolines, as demonstrated by the results. Condensation products of formaldehyde with desoxyvasicinone and amine fragments formed resulting from the cleavage of the initial molecule were isolated during the interaction of **3a** with formalin, which led to the occurrence of bis-compounds **4** and **5**. It is noteworthy that desoxyvasicinone **2a** having an active α-methylene group (CH_2-3) remains unchanged under the above-mentioned conditions.

Methylene-bis-mackinazolinone was not formed in a similar reaction with **3b**, though the breaking of the C_4=C_{12} bond accompanied by the generation of stable monomer **2b** and bis-amine **4** happened.

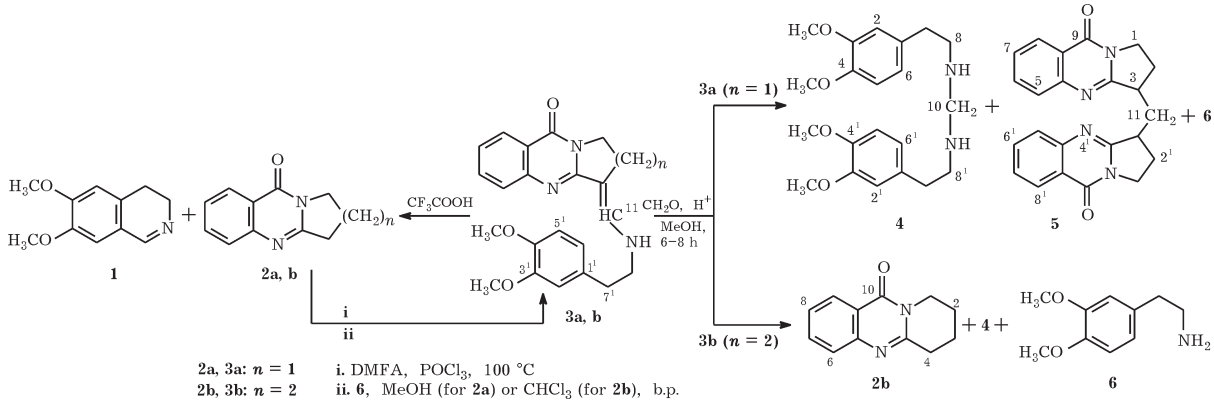
The structure of synthesized compounds **3a,b, 4–6** was confirmed by spectral data.Intense absorption bands of the amine (3437–3349 cm^{-1}) and carbonyl (1693–1650 cm^{-1}) groups of quinazoline fragments are present in IR spectra of derivatives of quinazolines **3a,b**. There are signals of H-11 at δ = 8.69 ppm for **3a** and H-12 at δ = 6.58 ppm for **3b** in ^{1}H NMR spectra.

The study of the structure of compounds **4** and **5** demonstrated that they were new compounds: *N*,*N*′-bis(3,4-dimethoxyphenylethyl)methanediamine **4** (26 %) and 3,3′-methylenebis(2,3-dihydropyrrolo[2,1-b]quinazoline-9-one) **5** (29 %). The corresponding values of 375 $[M + H]^+$ (for **4**) and *m*/*z* 385 $[M + H]^+$ (for **5**) were obtained by High Performance Liquid Chromatography/ Mass Spectrometry (HPLC/MS).

To assign signals in NMR spectra of compounds **4** and **5** spectral data for desoxyvasicinone **2a** and 3,4-dimethoxyphenylethylamine **6** were used. The PMR spectrum of compound **5** is characterized by the presence of H-1,1′ protons at 4.03 ppm (dt), 4.32 ppm (ddd), H-2,2′ at 2.09 ppm (dq), 2.51 ppm (dtd) and methyne protons H-3,3′ at 3.55 ppm (q). The proton signals of the methylene bridge appear as triplets at 3.55 (in compound **4**) and at 2.37 ppm (in **5**), which confirms the structure of **4** и **5** (Scheme 1).

EXPERIMENTAL

Infra-red spectra were recorded using a Perkin Elmer System 2000 FTIR Spectrometer in KBr pellets. Proton NMR spectra were registered on UNITY-400 spectrometers using HDMS as internal standard. The solvents were $CDCl_3$ and CD_3OD. The R_f values were determined by the TLC method using LS 5/40 silica gel plates and $CHCl_2$/MeOH = 14 : 1 (**I**) and C_6H_6/MeOH = 4 : 1 (**II**) elution systems.



Scheme 1.

Mass spectra were produced by an Agilent Technologies 6420 Triple Quad LC/MS mass spectrometer (electrospray ionization +ESI TIC Scan).

Melting points of all the synthesized compounds were determined on a Boethius microtable.

Desoxyvasicinone, mackinazolinone, 3-hydroxymethylidene-1,2,3,9-tetrahydropyr-rolo[2,1-b]-quinazoline-9-one, and 4-formyl-1,2,3,4-tetrahydropyrrolo[2,1-b]-quinazoline-10-one were obtained according to the known methods [11].

3-Hydroxymethylidene-1,2,3,9-tetrahydropyr-rolo[2,1-b]-quinazoline-9-one. Yield of 81 %, m.p. 214–218 °C ($CHCl_3$) [17].

4-Formyl-1,2,3,4-tetrahydropyrrolo[2,1-b]-quinazoline-10-one. Yield of 91 %, m.p. 201–203 °C (C_6H_{14}) [11].

3-(3,4-Dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one (3a). To a solution of 0.903 g (4.99 mmol) of 3,4-dimethoxyphenylethylamine in 10 mL of methanol, 1.068 g (4.99 mmol) of 3-hydroxymethylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one was added, the resulting mixture was refluxed on a water bath for 5 h. The reaction was monitored by TLC. The reaction mixture was cooled and the precipitated crystals were washed with methanol 3 times and air-dried. Yield of 1.55 g (82 %), m.p. 179–181 °C (MeOH), R_f 0.64 (system **I**).

The IR spectrum (KBr, ν, cm^{-1}): 3437(NH), 2934 (CH_2), 1693 (C=O), 1626 (C=N), 1573, 1518 (C=C), 1482 (C–H), 1375, 1325 (C–N), 1275, 1238, 1204.

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$ + CD_3OD, δ, ppm, *J*/Hz): 2.77 (2H, t, *J* = 8.2, H-2), 2.87 (2H, t, *J* = 7.2, H-7′), 3.62 (2H, t, *J* = 7.1, H-8′), 3.76 (3H, s, 3′-OCH_3), 3.82 (3H, s, 4′-OCH_3), 4.17 (2H, t, *J* = 8.2, H-1), 6.72 (1H, d, *J* = 7.9, H-5′), 6.76 (1H, d, *J* = 7.9, H-6′), 6.78 (1H, s, H-2′), 7.30 (1H, t, *J* = 7.5, H-7), 7.65 (1H, t, *J* = 7.4, H-6), 7.73 (1H, d, *J* = 8.2, H-5), 8.03 (1H, d, *J* = 7.9, H-8), 8.69 (1H, s, H-11).

4-(3,4-Dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrido[2,1-b]-quinazoline-10-one (3b). To 0.903 g (4.99 mmol) of a solution of 3,4-dimethoxyphenylethylamine in 10 mL of chloroform, 1.068 g (4.99 mmol) of 4-(formyl)-methylene-1,2,3,4-tetrahydropyrido[2,1-b]-quinazoline-10-one and the resulting mixture was heated on a water bath for 4 h. The reaction was monitored by TLC. The reaction mixture is cooled and chloroform is evaporated under vacuum, the residue is treated with a mixture of methanol/chloroform (10 : 1). The precipitated crystals are filtered, washed with methanol 4 times and air-dried. Yield of 1.30 g (87 %), m.p. 147–149 °C (MeOH/$CHCl_3$ = 10 : 1), R_f 0.64 (system **II**).

The IR spectrum (KBr, ν, cm^{-1}): 3349 (NH), 1650 (C=O), 1609 (C=N), 1516 (C=C), 1467 (C–H), 1336, 1309 (C–N), 1261, 1230.

The ^{1}H NMR spectrum ^{1}H (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 1.86 (2H, q, *J* = 6.2, H-2), 2.39 (2H, t, *J* = 6.0, H-3), 2.79 (2H, t, *J* = 6.4, H-8′), 3.47 (2H, т, *J* = 6.4, H-7′), 3.72 (3H, s, 3′-OCH_3), 3.81 (3H, s, 4′-OCH_3), 3.95 (2H, t, *J* = 8.2, H-1), 6.58 (1H, d, *J* = 12.2, H-12), 6.70 (1H, d, *J* = 1.8, H-2′), 6.72 (1H, dd, *J* = 1.8, 8.0, H-6′), 6.75 (1H, d, *J* = 8.0 H-5′), 6.91 (1H, d, *J* = 8.2, H-6), 7.13 (1H, t, *J* = 8.0, H-8), 7.46 (1H, t, *J* = 8.2, H-7), 8.08 (1H, d, *J* = 8.0, H-9), 9.86 (1H, m, NH).

Reaction of 3-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one (3a) and formaldehyde. To a solution of 0.3 g (0.79 mmol) of 3-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one **3a** in 10 mL of methanol, conc. HCl, then 0.07 mL (0.79 mmol) of a 30 % formalin solution (*d* = 1.092) were added dropwise to pH 4–5, and the resulting mixture was heated on a water bath for 8 h. Afterwards, the reaction mixture was cooled, alkalinized with ammonia to pH 9–10, the amine was exhaustively extracted with chloroform. The crude product was purified on a silica gel column using elution systems chloroform/methanol (100 : 0.5 → 100 : 5). Three products were obtained.

***N,N′*-Bis(3,4-dimethoxyphenylethyl)methanediamine (4), $C_{21}H_{30}N_2O_4$.** Yield of 80 mg (26 %), oil, R_f 0.22 (system **I**).

The IR spectrum (KBr, ν, cm^{-1}): 3429 (NH), 2924 (C–N), 2853 (C–O), 1605, 1519 (C=C), 1464, 1446 (C–H), 1254, 1239.

The ^{1}H NMR spectrum: (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.96 (4H, t, *J* = 7.1, H-7, 7′), 3.16 (4H, t, *J* = 6.9, H-8, 8′), 3.55 (2H, t, *J* = 6.6, CH_2-10), 3.74 (6H, s, 3, 3′-OCH_3), 3.77 (6H, s, 4, 4′-OCH_3,), 6.70 (6H, m, H-2, 2′, 5, 5′, 6, 6′).

The mass spectrum +ESI TIC Scan Frag 85.0V: 375 $[M+H]^+$.

3,3′-Methylene-bis(2,3-dihydropyrrolo[2,1-b]quinazoline-9-one) (5), $C_{23}H_{20}N_4O_2$.

Yield of 90 mg (29 %), m.p. 246–249 °C ($CHCl_3$) [17]. (MeOH/$CHCl_3$ = 10 : 1), R_f 0.44 (system **I**).

The IR spectrum (KBr, ν, cm^{-1}): 3435, 1667 (C=O), 1612 (C=N), 1560, 1516 (C=C), 1466 (C–H), 1384 (CH_2).

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.09 (2H, dq, *J* = 12.8, 8.4, H_a-2, 2′), 2.51 (2′, dtd, *J* = 12.4, 4.0, 8.0, H_e-2, 2′), 2.37 (2H, t, *J* = 7.8, H-11), 3.55 (2H, q, *J* = 7.8, H-3, 3′), 4.03 (2H, dt, *J* = 12.3, 7.9, H_a-1, 1′), 4.32 (2H, ddd, *J* = 12.6, 4.1, 8.6, H_e-1, 1′), 7.33 (2H, dt, *J* = 7.6, 1.0, H-7, 7′), 7.51 (2H, d, *J* = 7.8, H-5, 5′), 7.60 (2H, dt, *J* = 1.4, 7.7, H-6, 6′), 8.15 (2H, dd, *J* = 1.3, 8.0, H-8, 8′).

The ^{13}C NMR spectrum (δ, ppm): 26.67 (C-1, 1′), 34.55 (C-2, 2′), 41.82 (C-3, 3′), 44.86 (C-11), 120.88 (C-6, 6′), 126.49 (C-7, 7′), 126.52 (C-5, 5′), 126.58 (C-8, 8′), 127.08 (C-8a, 8′a), 134.29 (C-4a, 4′a), 149.18 (C-3a, 3′a), 161.07 (C-9, 9′).

The mass spectrum +ESI TIC Scan Frag135.0V: 385$[M + H]^+$.

3,4-Dimethoxyphenylethylamine (6), $C_{10}H_{15}NO_2$. Yield of 30 mg (20 %), oil, R_f 0.14 (system **I**).

The IR spectrum (KBr, ν, cm^{-1}): 3574, 3364, 3299 (NH_2), 3000, 2937 (C–N), 2836 (C–O), 1591, 1516 (C=C), 1464, 1418 (C–H), 1259, 1236 (C–O), 1156, 1142, 1028.

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.98 (2H, t, *J* = 7.2, H-7), 3.18 (2H, t, *J* = 7.2, H-8), 3.75 (3H, s, 3-OCH_3), 3.78 (3H, s, 4-OCH_3,), 6.71 (3H, m, H-2, 5, 6), 8.21 (2H, br. s, NH_2).

Reaction of 4-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,4-tetrahydropirido[2,1-b]-quinazoline-10-one (3b) and formaldehyde. To a solution of 50 mg (1.2 mmol) of 4-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,4-tetrahydropyrido[2,1-b]-quinazoline-10-one **3b** in 15 mL of methanol, conc. HCl, and then 0.12 mL (1.2 mmol) of a 30 % formalin solution (*d* = 1.092) were added dropwise and heated on a water bath for 6 h. The reaction was monitored by TLC. The reaction mixture was treated in a similar fashion to compound **3a**, yielding 20 mg (9 %) of 3,4-dimethoxyphenyl (9 %) of 3,4-dimethoxyphenylethylamine (**6**), 90 mg (19 %) of *N*,*N*′-bis(3,4-dimethoxyphenylethylamine **4** and 70 mg (27 %) of mackinazolinone **2b**.

Mackinazolinone (2b), m.p. 98–99 °C (MeOH), R_f 0.78 (system **II**).

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 1.92 (4H, m, H-2, 3), 2.94 (2H, t, *J* = 6.6, H-1), 4.02 (2H, t, *J* = 6.2, H-4), 7.36 (1H, dt, *J* = 1.1, 7.7, H-8), 7.54 (1H, d, *J* = 8.2, H-6), 7.65 (1H, dt, *J* = 1.6, 7.7, H-7), 8.21 (1H, dd, *J* = 1.6, 8.0, H-9) [18].

CONCLUSION

Thus, it was demonstrated that the interaction of 3-(3,4-dimethoxyphenylethylamino)-methylene-1,2,3,9-tetrahydropyrrolo[2,1-b]-quinazoline-9-one **3a** (*n* = 1) and formalin in acid medium did not give a cyclization product, and led to the formation of desoxyvasicinone and 3,4-dimethoxyphenylethylamine dimers, while elimination of the quinazoline fragment with the formation of mackinazolinone **2b** occurred in case of 4-(3,4-dimethoxyphenylethylamino)-methylidene-1,2,3,4-tetrahydropyrido[2,1-b]-quinazoline-10-one **3b** (*n* = 2).

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