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# **Selective Bromination of Tricyclic Quinazolones**

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#### Abstract

Bromination of the tricyclic quinazolones – deoxyvasicinone (1,2,3,9-tetrahydropyrrolo[2,1-b]quinazolin-9-one, 1), mackinazolinone (2,3,4,10-tetrahydropyrido[2,1-b]quinazolin-10-one, 2), 8-nitromackinazolinone (8-nitro-2,3,4,10-tetrahydropyrido[2,1-b]quinazolin-10-one, 3) and their some analogues have been systematically studied. It was found that depending on the reaction conditions and structures of the starting compounds takes place bromination on the aromatic ring, on N1=C2 double bound of pyrimidine ring or on methylene groups of the  $\alpha$ -position (C-4). Selective bromination of 8-nitromackinazolinone (3) was investigated by N-bromosuccinimide (NBS) in the presence of benzoyl peroxide (BZP) in anhydrous tetrachloromethane. It was developed the method for monobromination of initial compound. The synthesized optical isomers of (*R*, *S*)-4-bromo-8-nitromackinazolinone (16) are quantitatively separated on HPLC column, consisting chiral adsorbent. Bromination direction and a course of the reactions with inorganic bromates, molecular bromine and N-bromosuccinimide were discussed. It was revealed that using allylic bromination method (*Wohl-Ziegler Reaction*) for compound 3 gives exclusively and in high yield targeted chiral compound - (*R*, *S*)-4-bromo-8-nitromackinazolinones (16).

Keywords: 8H (nitro)-mackinazolinones, activated methylene group, selective bromination, optical isomers, chiral column.

#### Introduction

Tricyclic quinazoline alkaloids (deoxyvasicinone, 1; mackinazolinone, 2) are widely distributed in nature [1-4]. There are many review articles, which covered bi- and tricyclic quinazoline alkaloids [5-10] and their substituted derivatives. These compounds have different reaction centers: nitrogen atoms, carbonyl and activated methylene groups, a benzene ring [12] (Fig. 1).



Fig. 1: Starting tricyclic quinazoline alkaloids.

These centers can react with electrophilic and nucleophilic reagents, resulting in different derivatives of tricyclic quinazoline alkaloids [13-17]. Tricyclic quinazolines exhibit different properties [18-21]; it is often found that several of the quinazoline compounds possess more significant biological activity than the corresponding quinazolones. Along with this, the number of methylene groups have a positive effect on the biological activity; so increasing of the number of the methylene groups (2, 3-tri  $\rightarrow$  2, 3-tetra  $\rightarrow$  2, 3-penta  $\rightarrow$  2, 3-hexamethylene quinazolines) increases the biological activity of the compounds [22].

# **Materials and Methods**

Research objects of this work are tricyclic quinazolones, in particular deoxyvasicinone (1), mackinazolinone (2) and 8nitromackinazolinone (3) and their analogues. Research methods are organic synthesis reaction, such as cyclization, nitration, electrophilic substitution (mono-, and dibromination); NBS is used as selective brominating agent; structural analysis of the synthesized compounds by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra, qualitative separation of optical isomers using column chromatography (HPLC) in presence of chiral adsorbent.

Synthesized new (*R*, *S*)-4-bromo-8-nitromackinazolinone (16) was screened by HPLC (Agilent 1100 Series, USA) using a column with chiral adsorbent - amylose *tris*-[(*S*)- $\alpha$ -methyl-benzylcarbamate] coated on 10µm silica-gel (ChiralPak® AS 0.46cm  $\phi$  x25cm, DAIC 20025, Daicel Chemical Industries, LTD, France), and mobile phase A - ACN, and B - i-PrOH in gradient mode: 0-10min B2% to 10% and 10-15min B10%.

<sup>1</sup>H-NMR spectra were recorded in CDCl<sub>3</sub> on Varian 400-MR spectrometer operating accordingly at 400 MHz. Tetramethylsilane (TMS) was used as internal standard, chemical shifts  $\delta$  of <sup>1</sup>H were recorded in ppm. Mps were measured on a Boethius and MEL-TEMP apparatus manufactured by Branstead international (USA) and were uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 and IR Fury System 2000 (Perkin-Elmer) as KBr pellets. HPLC analysis was acquired on a Agilent 1200 series. The reaction process was monitored by TLC on Sorbfil and Whatman UV-254 percoated aluminum plates using C<sub>6</sub>H<sub>6</sub>/CH<sub>3</sub>OH (7:1) solvent system and developed plates were visualized under UV lamp, and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> or with the dried CaCl<sub>2</sub>.

Deoxyvasicinone (1), mackinazolinone (2) and 8nitromackinazolinone (3) were prepared by the literature method [23].

**Deoxyvasicinone** (1): Yield 75 %, mp=110-111°C (hexane).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.25 (q, *J*=7.8 Hz, 2H, CH<sub>2</sub>-2), 3.15 (t, *J*=7.8 Hz, 2H, CH<sub>2</sub>-3), 4.20 (t, *J*=7.4 Hz, 2H, CH<sub>2</sub>-1), 7.40 (td, *J*=1.2 Hz, J=8.0 Hz, 1H, H-7), 7.60 (d, *J*=8.0 Hz, 1H, H-5), 7.71 (td, *J*=1.3 Hz, *J*=8.0 Hz, 1H, H-6), 8.22 (dd, *J*=1.2 Hz, *J*=8.0 Hz, 1H, H-8) ppm.

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>): δ = 19.0 (C-2), 32.1 (C-3), 46.2 (C-1), 119.6 (C-7), 125.1 (C-8a), 126.1 (C-5), 126.6 (C-8), 133.3 (C-6), 147.4 (C-4a), 158.7 (C-9), 160.1 (C-3a) ppm.

**Mackinazolinone** (2): Yield 85 %, mp=98-99°C (hexane). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 8.28 (dd, *J*=1.28 Hz, *J*=7.92 Hz, 1H, H-9), 7.74 (td, *J*=1.56 Hz, *J*=8.4 Hz, 1H, H-7), 7.62 (d, *J*=7.92 Hz, 1H, H-6), 7.44 (td, *J*=1.04 Hz, J=8.04 Hz, 1H, H-8), 4.1 (t, *J*=6.12 Hz, 2H, CH<sub>2</sub>-1), 3.00 (t, *J*=6.72 Hz, 2H, CH<sub>2</sub>-4), 2.05-1.96 (m, 4H, CH<sub>2</sub>-2,3) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.3 (C-3), 22.1 (C-2), 31.9 (C-4), 42.3 (C-1), 120.4 (C-8), 126.1 (C-9a), 126.4 (C-6), 126.6 (C-9), 134.2 (C-7), 147.4 (C-5a), 154.9 (C-10), 162.2 (C-4a) ppm.

## 8-Nitromackinazolinone (3).

In 8 ml (95.72%,  $\rho$ =1.835 g/cm<sup>3</sup>) of concentrated sulfuric acid with vigorous stirring and cooling (ice bath) dissolved

4 g (20 mmol) mackinazolinone (1), then at the temperature below 2°C was added drop wise nitrating mixture, consisting of 3 ml nitric (59.69%,  $\rho$ =1.365g/cm<sup>3</sup>) and 3 ml of sulfuric ( $\rho$ =1.835 g/cm<sup>3</sup>) acids. After that mixture was stirred at the temperature of 5-10°C and 1 h at room temperature. Reaction mixture treated by ice and the formed yellow precipitates filtered off, washed with water to neutral medium and dried.

Yield 4.55 g, 92 %, mp 183-184°C (methanol).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$ = 9.15 (d, *J*=2.6 Hz, 1H, H-9), 8.51 (dd, *J*=2.68 Hz, *J*=8.96 Hz, 1H, H-7), 7.71 (d, *J*=9.0 Hz, 1H, H-6), 4.12 (t, *J*=6.16 Hz, 2H, CH<sub>2</sub>-1), 3.07 (t, *J*=6.72 Hz, 2H, CH<sub>2</sub>-4), 2.1-1.9 (m, 4H, CH<sub>2</sub>-2,3) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 19.1 (C-3), 21.9 (C-2), 32.2 (C-4), 42.9 (C-1), 120.3 (C-8), 123.5 (C-9a), 128.0 (C-6), 128.2 (C-9), 145.1 (C-7), 151.5 (C-5a), 158.7 (C-10), 161.1 (C-4a) ppm.

# General procedure for selective bromination: Synthesis of (*R*, *S*)-4-bromo-8-nitro-mackinazolinone (16)

The reaction mixture, consisting 0.5 g (2 mmol) of 8nitromackinazolinone (3), 0.43 g (2.4 mmol) of NBS and 0.04 g (0.2 mmol) of benzoyl peroxide in 15 ml of tetrachloromethane refluxed for 8 h and was left overnight. The formed precipitate of succinimide was filtered off, and solvent was evaporated in vacuo. The residue was treated with water and the resulting crystals were filtered off, washed with water and dried. 0.61 g (92%) product (**16**) has been synthesized, mp 136-137°C (ethanol), Rf=0.6 (benzene:methanol – 7:1).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.10 (d, *J*=2.2 Hz, 1H, H-9), 8.43 (dd, *J*=2.2 Hz, *J*=8.8 Hz, 1H, H-7), 7.60 (d, *J*=8.8 Hz, 1H, H-6), 4.09 (t, *J*=6.0 Hz, 2H, CH<sub>2</sub>-1), 3.0 (t, *J*=6.1 Hz, 1H, CH<sub>2</sub>-4), 1.97-1.90 (m, 4H, CH<sub>2</sub>-2,3) ppm.

<sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>):  $\delta$  = 18.6 (C-3), 20.8 (C-2), 31.3 (C-4), 41.7 (C-1), 119.4 (C-8), 121.4 (C-9a), 127.3 (C-6), 127.8 (C-9), 144.3 (C-7), 150.4 (C-5a), 157.5 (C-10), 160.5 (C-4a) ppm.

IR, v (cm<sup>-1</sup>): 2956 (C-H), 1670 (CO), 1580 (C=N), 1550 (C-N), 1505 (NO<sub>2</sub>), 672 (C-Br).

## **Results and discussion**

Aromatic and heterocyclic compounds containing a bromine atom in the ring are of considerable importance for organic synthesis.

It is known, that sodium or potassium bromates are a powerful brominating agents for aromatic compounds that contain deactivating substituents [24].

Bromination of tricyclic quinazolines by different brominating agents (sodium/or potassium bromates, molecular bromine, NBS) has been studied.

**For example:** it was studied aromatic bromination of tricyclic quinazolones (1, 2) in sulfuric acid, and was revealed that in this case takes place aromatic electrophilic substitution in benzene ring [21] (Scheme 1):



Scheme 1: Bromination by inorganic bromates.

We previously studied the interaction of some tricyclic quinazolones with molecular bromine. Reaction goes on C=N double bond and are formed appropriate perbromides. Reaction carried out in the ratio of reagents 1:2 in dry chloroform at  $0-5^{\circ}$ C and corresponding perbromides (6, 7)

have been synthesized. Conducted chemical transformations of the obtained perbromides under the influence of sodium bicarbonate and acetone; wherein hydrobromides (8, 9) and bromine complexes (10, 11) are received [25] (Scheme 2):



Scheme 2: Bromination by molecular bromine and modification of formed perbromides.

The received perbromides when stored under normal conditions loss of bromine molecule and turn into hydrobromides. Treating of perbromides with acetone takes place bromination of acetone and occurs with formation of bromacetone and are formed the precipitates of the corresponding hydrobromides (8, 9), which under the action of aqueous ammonia is easily transferred to the starting compounds 1, 2. Perbromides 6, 7 easily converted into bromine complexes (10, 11) under the action of 5% sodium bicarbonate. Heating of perbromides in aqueous acetic acid are formed a mixture of the mono- (12, 13) and dibromo- (14, 15) derivatives.

To obtain the targeted monobromo – derivatives, which contain asymmetrical centre we studied the reaction of 8nitromackinazolinone with N-bromosuccinimide. The reaction carried out in dried tetrachloromethane in the presence of benzoyl peroxide (BZP) by refluxing for 8 h of mixture of NBS and 8-nitromackinazolinone (3). As a result of this reaction exclusively and in high yield (92%) of monobromo derivative - 4-bromo-8-nitromackinazolinones (16) have been synthesized (Scheme 3):



Scheme 3: Allylic bromination of quinazolones.

N-Bromosuccinimide (NBS) is a brominating agent that is used as source for bromine in radical reactions (for example: allylic bromination - *Wohl-Ziegler Reaction*) and various electrophilic additions. The bromination of allylic positions with N-bromosuccinimide (NBS) follows a radical pathway.

The synthesized compound 16 can be in two forms of optical isomers, as 4-(R)-16a and 4-(S)-bromo-8-nitromackinazolinones (16b) (Fig. 2):



Fig. 2: Optical isomers of compound 16.

Using HPLC equipped with a chiral column, we qualitatively separated two optical isomers with RT 7.187 (51.5579%) and 7.468 (47.2074%), respectively (Fig. 3)



Fig. 3: HPLC results of the separated optical isomers.

# Conclusion

Comparative bromination of the tricyclic quinazolines (1-3) and their some analogues with different bromating agents inorganic bromates, molecular bromine and Nbromosuccinimide (NBS) have been studied and discussed. It was found that depending on the reaction conditions and structures of the starting compounds and bromating agents takes place bromination on the aromatic ring, on N1=C2 double bound of pyrimidine ring or on methylene groups of the α-position (C-4). Targeted bromination of 8nitromackinazolinone (3) was investigated by Nbromosuccinimide (NBS) in the presence of benzoyl peroxide (BZP) in anhydrous tetrachloromethane and was developed the method for monobromination. Such selective monobromination of 8-nitromackinazolinone in the participation only of  $\alpha$ -CH<sub>2</sub> group was shown. The synthesized optical isomers of (R,S)-4-bromo-8nitromackinazolinone is quantitatively separated on HPLC column, consisting chiral adsorbent. It was revealed that using allylic bromination method (Wohl-Ziegler Reaction) for compound 3 gives exclusively and in high yield (*R*,*S*)-4-bromo-8targeted chiral compound nitromackinazolinone (16).

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