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# NOVEL α-METHYL(BENZYL)DEOXYVASICINONES

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*A method was developed to prepare α-methyl(benzyl)deoxyvasicinones by alkylation of α-hydroxymethylidenedeoxyvasicinone. It has been shown that the reaction proceeds anomalously through a deformylation step.*

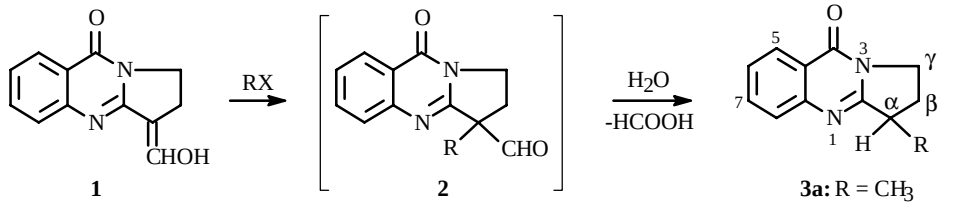
**Key words:** deoxyvasicinone, quinazoline alkaloids, alkylation, deformylation.

Many quinazoline derivatives are used in medical practice [1-3]. Therefore, tricyclic quinazoline alkaloids isolated from *Peganum harmala* are of great interest [4]. Among them, deoxypeganine (2,3-trimethylene-3,4-dihydroquinazoline), which is recommended as an anticholinesterase preparation, is used in medicine.

Deoxypeganine and its derivatives are isolated from plants or produced by several methods [6, 7]. The main synthetic method is reduction of deoxyvasicinone (DOV) by zinc in acidic medium [8, 9]. DOV itself is also isolated from natural sources or synthesized by condensation of anthranilic acid and γ-butyrolactam [10].

A large number of DOV derivatives and analogs were synthesized by this method. However, the known methods are unsuitable for synthesizing DOV derivatives with alkyl and arylalkyl groups in the α-position because the α-alkyl(arylalkyl)-γ-butyrolactams required for condensation with anthranilic acid are rather difficultly accessible.

By studying the alkylation of α-hydroxymethylidenedeoxyvasicinone (**1**), which was prepared by reaction of deoxyvasicinone with Vilsmeier—Haack reagent (phosphoryl chloride + dimethylformamide), we unexpectedly observed a new phenomenon, simultaneous C-alkylation and loss of hydroxymethylidene. As it turned out, either α-methoxy-(benzyloxy)methylidenedeoxyvasicinone (**4**) or N-methyl(benzyl)-α-formyldeoxyvasicinone (**5**) are formed during the methylation and benzylation of **1**. However, alkylation of **1** by the alkylating agents mentioned above gives α-methyl- and benzyldeoxyvasicinones (**3a** and **b**), i.e., the deformylation products of α-methyl(benzl)- and α-formyldeoxyvasicinones (**2**).




**1** **2**

**3a:** R = $CH_3$

**b:** R = $CH_2C_6H_5$

Such behavior of **1** is explained by initial alkylation of it to form α-methyl(benzyl)- and α-formyldeoxyvasicinones, which lose under the reaction conditions a molecule of formic acid, giving α-methyl- and α-benzyldeoxyvasicinones (**3a** and **b**).

Alkylation of **1** can theoretically proceed in three directions because it can exist under the reaction conditions as the enol (**1a**), the aldehyde (**1b**), or the enaminoaldehyde (**1c**).

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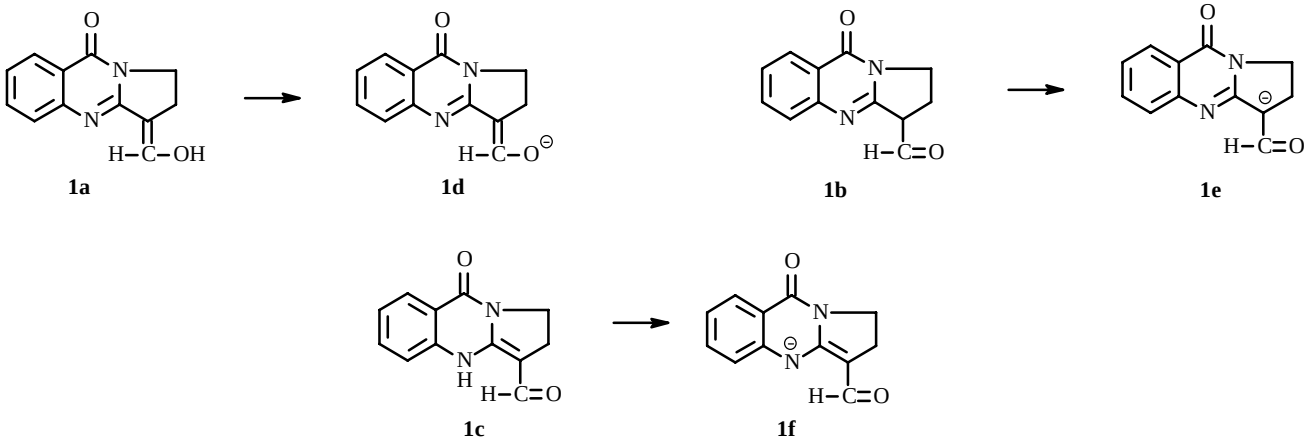
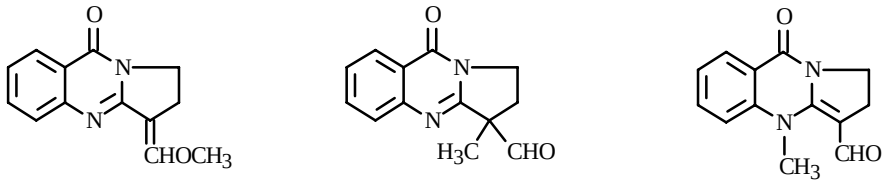


**1a** **1d** **1b** **1e**

**1c** **1f**

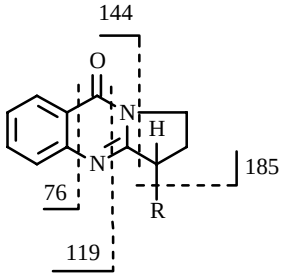
Base converts **1a-c** into the corresponding anions **1d-f**, which are alkylated. Methylation can form $\alpha$-methoxymethylidene (**4**), $\alpha$-methyl-$\alpha$-formyl (**2**), and N-methyl-$\alpha$-formyldeoxyvasicinones (**5**), which can also be deformylated to form the corresponding deoxyvasicinone, **3a**, and N-methyl-1H-2,3-dehydrodeoxyvasicinone.



**4** **2** **5**

The structures of **3a** and **3b** were unambiguously confirmed and a final decision between structures of **2**, **3**, **4**, and **5** was made by studying their IR, PMR, and mass spectra. Thus, IR spectra of **3a** and **3b** contain carbonyl stretching vibrations at 1675-1681 $cm^{-1}$; C=N vibrations, 1614-1619 $cm^{-1}$, and C–N, 1562-1570 $cm^{-1}$.

Mass spectra (*m*/*z*) contain very strong molecular ions $[M]^+$ at 200 (**3a**) and 276 (**3b**) and fragments at 186, 185, 145, 144, and 119, which are characteristic of deoxyvasicinone and other quinazoline derivatives [11].



R = $CH_3$, $CH_2C_6H_5$

The PMR spectrum has signals for methyl protons of **3a** as a doublet at 1.4 ppm; $\alpha$-CH (**3a** and **b**) methine protons, 3.85-3.87 ppm (1H, multiplet); $\beta$-$CH_2$ (**3a** and **b**) methylene protons, 2.25-2.45 ppm (2H, multiplet); $\gamma$-$CH_2$ (**3a** and **b**) methylene protons, 4.1-4.15 ppm (2H, triplet); and $\alpha$-$CH_2$ protons (**3b**), 2.87 ppm (2H, doublet). These data unambiguously confirm the structures of the synthesized compounds (**3a** and **b**) and exclude structures **2**, **4**, and **5**.

Thus, a synthetic scheme that is new in principle for synthesizing $\alpha$-alkyl(arylalkyl)deoxyvasicinones and consists of formylation of deoxyvasicinone, alkylation of **1**, and preparation of $\alpha$-alkyl(arylalkyl)deoxyvasicinones was developed. This method can be further applied to the synthesis of $\alpha$-alkyl(arylalkyl)deoxypeganines by reduction of **3a** and **3b**.

Formylation of deoxyvasicinone forms **1**, $\alpha$-dimethylaminomethylidenedeoxyvasicinone, or $\alpha$-dimethylammoniummethylidenedeoxyvasicinone chloride, depending on the reaction conditions [12].

Our results indicate that purification of **1** is often difficult owing to the presence of small amounts of the last two compounds. We developed a purification method that involves treatment of the reaction mixture after completion of the reaction with a comparatively small amount of water. Then, the resulting solid is separated and mixed with saturated NaOAc solution at room temperature for 3-4 h. Such treatment of the reaction mixture increased the yield of **1** from 70 to 83%.

## EXPERIMENTAL

Mass spectra were recorded on a MS25RS (Kratos) instrument; IR spectra, Perkin—Elmer System 2000 IR-Fourier spectrometer (KBr disks); PMR spectra, Tesla BS 567A instrument at working frequency 100 MHz (internal standard TMS, δ scale) in $CD_3OD$ and $CDCl_3$ solutions.

**α-Hydroxymethylidenedeoxyvasicinone (1)** was prepared by a modification of the known method [12].

A vigorously stirred (mechanical stirrer) solution of freshly distilled anhydrous DMF (19.3 g, 0.27 mol) cooled in ice (water bath) was treated dropwise with phosphoryl chloride (16.7 g, 0.12 mol) and in portions with deoxyvasicinone (10 g, 0.054 mol). The reaction mixture was stirred for 2 h at room temperature, left overnight, heated for 2 h on a water bath (95-98°C), cooled, and decomposed with water (25 mL). The resulting solid was filtered off, placed in a reaction flask, treated with NaOAc solution (30%), and stirred at room temperature for 3-4 h. The resulting white solid was filtered off and washed with water (3-4 times) to afford the reaction product (9.5 g, 83%), mp 206-208°C (acetone), lit. [12] mp 205-206°C.

**α-Methyldeoxyvasicinone (3a).** Ethanol (25 mL) was placed in a flask (100 mL) and treated with **1** (500 mg, 2.34 mmol) and NaOH (94 mg, 2.34 mmol). The mixture was stirred for 30 min, treated wth methyl iodide (0.3 mL, 4.8 mmol), and stirred at 75-80°C for 6 h. The resulting inorganic salt was filtered off. The solvent was removed. The solid was left for 3-4 h in a desiccator over $CaCl_2$. Recrystallization of the solid from hexane gave **3a** (300 mg, 65%), mp 120-121°C.

Mass spectrum (*m*/*z*, *I*, %): 200 (100), 186 (14), 185 (60) $[M - CH_3]^+$, 144 (6), 119 (64).

IR spectrum (ν, $cm^{-1}$): 1675 ($\nu_{C=O}$), 1614 ($\nu_{C=N}$), 1562 ($\nu_{C-N}$).

PMR spectrum ($CDCl_3$, δ, ppm): 8.12 (dd, H5), 7.3-7.8 (m, H-6), 7.3-7.8 (m, H-7), 7.3-7.8 (m, H-8), 3.85 [m, α(CH)], 2.45 (m, β-$CH_2$), 4.15 (t, γ-$CH_2$), 1.4 (d, α-$CH_3$).

**α-Benzyldeoxyvasicinone (3b)** was synthesized analogously by the above method from **1** (100 mg, 0.47 mmol), benzylchloride (0.1 mL, 0.82 mmol), and NaOH (20 mg, 0.47 mmol) to afford **3b** (73 mg, 57%), mp 78-79°C (hexane).

Mass spectrum (*m*/*z*, *I*, %): 276 (100), 199 (77), $[M - C_6H_5]^+$, 185 (9) $[M - CH_2C_6H_5]^+$, 145 (16).

IR spectrum (ν, $cm^{-1}$): 1681 ($\nu_{C=O}$), 1619 ($\nu_{C=N}$), 1570 ($\nu_{C-N}$).

PMR spectrum ($CD_3OD$, δ, ppm): 8.13 (dd, H-5), 7.25-7.85 (m, H-6), 7.25-7.85 (m, H-7), 7.25-7.85 (m, H-8), 3.87 [m, α(CH)], 2.25 (m, β-$CH_2$), 4.1 (t, γ-$CH_2$), 2.87 (d, α-$CH_2$).

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