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# Synthesis and Molecular Structure of 9–(Arylidene)amino–11–(2–hydroxyphenyl)–8–oxa–12–azatricyclo[7.3.1.0$^{2,7}$]trideca–2(7),3,5–trienes Formed by Cascade Reaction of 2,6–Di(2–hydroxyphenyl)–4–oxopiperidines with Arylaldehydes and Ammonia

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*Six novel 9-(arylidene)amino-11-(2-hydroxyphenyl)-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]-tridecatrienes incorporating formally 1,5-oxazocine moiety were synthesized by one step protocol from 2,6-di(2-hydroxyphenyl)-4-oxopiperidines with aromatic aldehydes and ammonium acetate.*

**Keyword:** Oxopiperidine, Petrenko-Kritchenko reaction, oxaazatricyclotridecanes, multicomponent condensation.

# Синтез и молекулярная структура 9–(арилиден)амино–11–(2–гидроксифенил)–8–окса–12–азатрицикло[7.3.1.0$^{2,7}$]тридека–2(7),3,5–триенов, образующихся каскадной реакцией 2,6–ди(2–гидроксифенил)–4–оксопиперидинов с ароматическими альдегидами и аммиаком

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*Шесть новых 9-(арилиден)амино-11-(2-гидроксифенил)-8-окса-12-азатрицикло[7.3.1.0$^{2,7}$]-тридекатриенов, формально включающих 1,5-оксазоциновое ядро, были синтезированы в одну стадию конденсацией 2,6-ди(2-гидроксифенил)-4-оксопиперидинов с ароматическими альдегидами и ацетатом аммония.*

**Ключевые слова:** Оксопиперидин, реакция Петренко-Критченко, оксаазатрициклотридекан, мультикомпонентная конденсация.

Multicomponent reactions of aromatic aldehydes with aliphatic ketones in the presence of ammonium acetate form a class of general Petrenko-Kritchenko domino reactions[1] and are widely used for the preparation of 2,6-diaryl substituted γ-piperidones,[2,3] which are important initial compounds in synthesis of biologically active agents.[4-7]

However, in the case of salicylic aldehyde (**SA**) this method does not result in corresponding piperidones. For example, when acetone or its homologues are used as a dialkylketone component, the main product of the cascade condensation would have structure of *ortho*-hydroxyphenylimino substituted benzopyranes.[8] Moreover, the derivatives of oxaazatricycloalkanes[9,10] particularly, benzopyranyl substituted 8-oxa-10-azatricyclo[7.3.1.0$^{2,7}$]tridecane[11,12] are formed in the multicomponent reaction of **SA** with a classic ethyl 3-oxobutanoate component and ammonium or methylammonium acetate.

The mixtures of **SA** with monophenylacetone[13] or with 1,3-diphenyl acetone[14] and ammonium acetate (taken in 2:1:2 proportion) did produce 2,6-di(2-hydroxyphenyl) substituted 3-phenylpiperidone[13] or 3,5-diphenylpiperidone,[14] though the reaction mixture also contained in the latter case 2-hydroxybenzylidenoamino substituted 8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]tridecane, separated later[15] individually and characterized by X-ray analyses in the free form[15] or as acetate ethanol disolvate[16] (Figure 1).

In this work, we continue our investigation to broaden the boundaries of the cascade method application for the preparation of 8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]tridecanes. First, in the one-step triple component condensation we used the mixtures of **SA** with monophenylacetone **1a** or 1-phenyl-4-(4-hydroxy)butan-2-one **1b** and ammonia in a considerable excess (in 3:1:5 proportion).

The expected new 8-oxa-12-azatricyclotridecanes **2a** and **2b** were separated with good yields. Asymmetrically substituted acetones **1** being used in this reaction, the possibility of formation of the two end compounds isomeric by their R substituent position (at C-10 or at C-13) arises. Stereoselectivity (rather at C-10 than at C-13) seems to be under sterical control. We suppose that 3-*R*-2,6-di(2-hydroxyphenyl)piperidones could be intermediates of the condensation reaction and thus could react further with the excess amount of **SA** and ammonia to give products such as the 8-oxa-12-azatricyclotridecanes **2a,b**. Indeed, the aminal-like structure showed sterically preferable *O*-nucleophilic heterocyclization by oxyphenyl substituent at C-6 of the piperidine cycle. The X-ray data of the known diphenyl substituted 8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]tridecane **2c** in the free form[15] or in acetate ethanol disolvate[16] both demonstrated that one benzoxy group connected with α-position of the piperidine cycle was condensed 1,3-diaxially with it, thus forming dihydropyranic nucleus, while another analogous 2-hydroxyphenyl group together with two phenyl groups at β-, β'-positions of the piperidine moiety were all equatorial. It witnessed for the Petrenko-Kritchenko reaction reversibility to produce sufficient quantity of the axially oriented α-2-hydroxyphenyl group in the synthesized intermediate piperidones.

It is worth mentioning that if in this cascade process 5-nitro derivative of **SA** was used instead of **SA** then the reaction leads to the corresponding piperidone, and no trace of benzoxazocine was fixed even by LC/MS analysis. This fact may supposedly be explained by tautomeric transformation of the 5-nitro-**SA** into its nitrooxamic derivative with iminoquinoid structure incapable of participating in *O*-nucleophilic heterocyclization.

To prove the proposed novel route for the preparation of the one known substance **2c** and new 8-oxa-12-azatricyclotridecanes **2d-g** we studied the condensation of 3,5-diphenyl-2,6-di(2-hydroxyphenyl)piperidone[14] **3** not only with **SA** but also with nitrobenzaldehydes or *N,N*-dimethylaminobenzaldehyde **4c-g** and ammonium acetate.

In fact, carrying out the condensation with a **3**: OCH-$C_6H_4$-R:$NH_4OAc$ ratio = 1:1:1.3 (at 20 °C, 72 h, using alcohol in the presence of acetic acid) gave rise to a cascade formation of the correspondingly substituted 8-oxa-12-azatricyclotridecanes **2c** and **2d-g** which can be separated from the mixture by crystallization in 67 % yield (for compound **2c**) and in 41–51 % (for compounds **2d-g**). All the characteristics of the compound **2c** coincided with those of the known sample.

All oxaazatricyclotridecanes **2a**,**b**,**d-g** are new and their structures were confirmed by $^1$H NMR, IR, LCMS (ionization or electron impact) analysis.

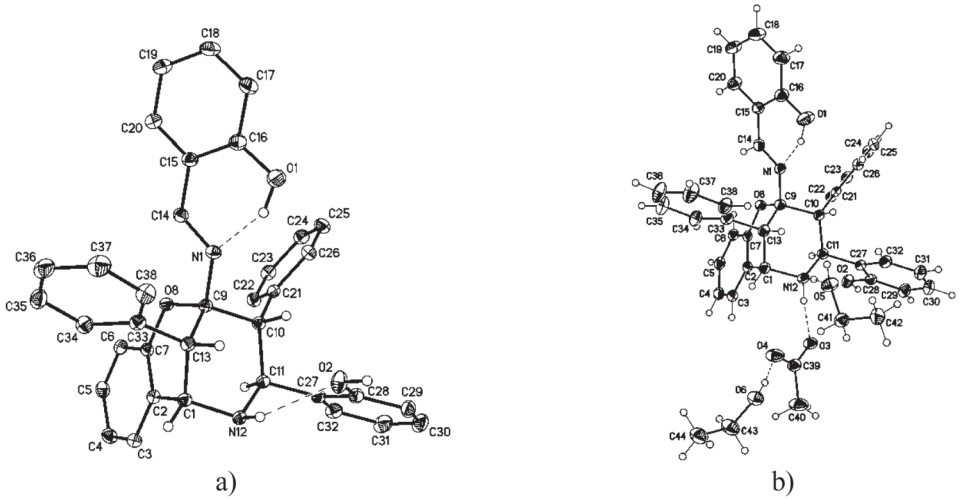
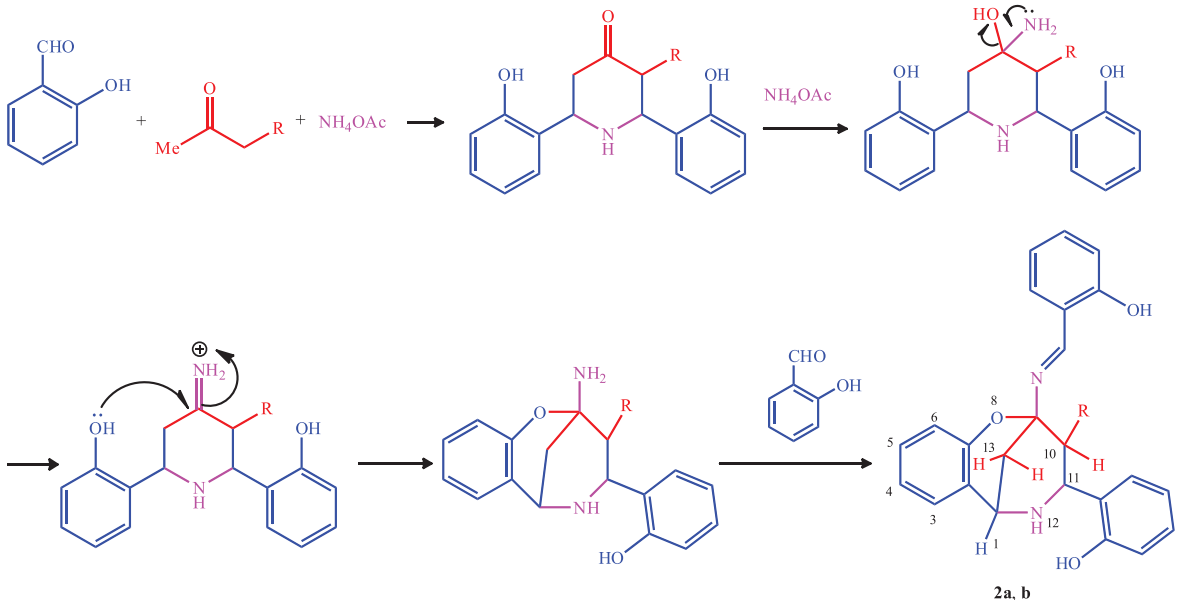
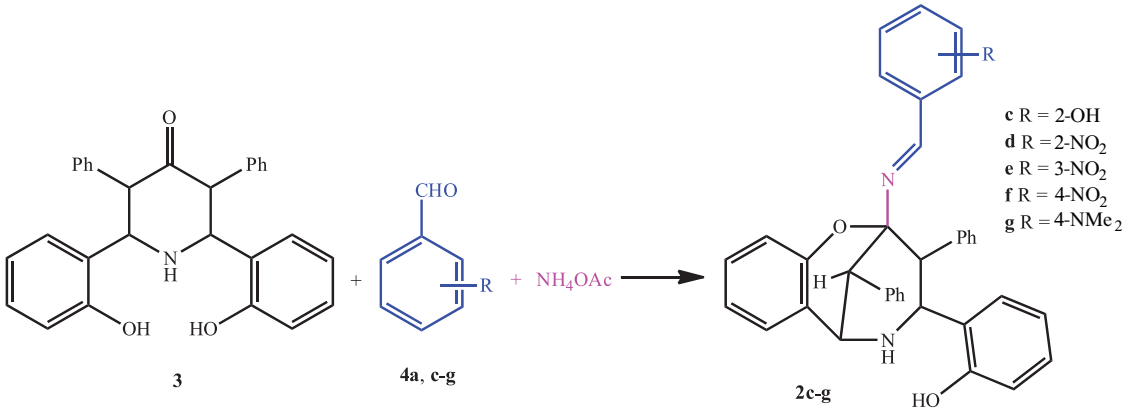



**Figure 1.** a) Molecular structure of compound **2c**; b) Molecular structure of compound **2c** in acetate ethanol solvate.




**Scheme 1**.




**Scheme 2**.

We tested the compounds **2b, 2c** for *in vitro* antibacterial (on *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Staphylococcus aureus bacteria*), antifungial (*Aspergillus niger*, *Fusarium oxysporum*, *Candida albicans* and *Saccharomyces cerevisiae fungi*) and cytotoxic (on Human hepatocellular carcinoma, Lung cancer and Human rhabdomyosarcoma cell lines) activities. Compound **2b** and **2c** exhibited substantial level (50 %) of antibacterial activity only on bacteria *B. subtilis* (**2c**) and on *S. aureus* (**2b**). Both compounds showed no notable activities on the other tests.

## Experimental

Melting points were determined in open capillary tubes on a digital Stuart SMP3 apparatus. Elemental analysis was conducted on Euro Vector EA-3000 analyzer. IR spectra were recorded in KBr disks on an Infralum FT-801 spectrometer. The $^1$H NMR spectra were recorded on a Bruker WP-400 instrument in $CDCl_3$, TMS as internal standard. LC/MS analysis was performed using an Agilent 1100 series chromatograph equipped with Agilent 1100 series DAD (wavelength 254±4 nm was used for detection), Sedex 75 ELSD and Agilent LC/MSD VL mass spectrometer (ionization in ESI mode).

X-Ray structural analysis of compound **2c** (free form and disolvate form) was measured on an APEX2 (Bruker, 2005). All X-ray analyses and calculations were carried out with SAINT (Bruker, 2001) and SHELXTL (Sheldrick, 2008).

Crystallographic data for compound **2c** have been deposited with the Cambridge Crystallographic Data Center (CCDC 800614 for free form **2c** and CCDC 815515 for disolvate **2c**·$CH_3COOH$·$C_2H_5OH$). They contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

*Synthesis of 9-arylidenamino-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$] trideca-2(7),3,5-trienes **2a-g** (general procedures).*

*Method A.* A solution of ketone **1b** (0.82 g, 5.00 mmol), salicylaldehyde (**SA**) (1.83 g, 15.00 mmol), and ammonium acetate (2.0 g, 33 mmol) in alcohol (40 ml) and acetic acid (2 ml) was stirred at ~20 ºC. The reaction was monitored by TLC and was completed in 30 h. The precipitate was filtered off, washed with alcohol (10 ml) and ether (10 ml), purified by column chromatography and recrystallized from alcohol to obtain the pure oxaazatricyclotridecatriene **2a**,**b**.

*Method B.* Equimolar amounts of piperidone[14] **3** (1.00 g, 2.30 mmol), aromatic aldehyde **4c-g** (4.60 mmol) and ammonium

acetate (13 mmol) were refluxed in alcohol (40 ml) and acetic acid (2 ml). The reaction was monitored by TLC and was completed in 72 h. The precipitate was filtered off, washed with cold alcohol (10 ml) and ether (10 ml), purified by column chromatography and recrystallized from alcohol to obtain the pure 8-oxa-12-azatricyclotridecatriene **2c-g**.

*9-[(2-Hydroxybenzylidene)amino]-11-(2-hydroxyphenyl)-10-phenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2a***. Yield 22 %, mp 182-183 ºC. IR (KBr) ν cm$^{-1}$: 3396, 3290, 1637. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ ppm: 1.90 (br. s, 2H, $^+NH_2$), 2.00 and 2.80 (both d.d, 1H each, $^2J$ 13.0 Hz, $^3J$3.0 Hz, 2H-13), 3.55 (d, 1H, $^3J$ 11.5 Hz, H-10), 4.18 (d, 1H, $^3J$ 11.5 Hz, H-11), 4.45 (t, 1H, $^3J$ 3.0 Hz, H-1), 6.30-7.39 (m, 17H, H arom),8.35 (s,1H, N=CH), 10.50 (br. s, 1H, OH). MS, *m/z*: 463 $[M+H]^+$. Found (%): C,78.17; H, 5.54; N, 5.54. Calc. for $C_{30}H_{26}N_2O_3$ (%): C,77.92; H, 5.62; N,6.06.

*9-[(2-Hydroxybenzylidene)amino]-11-(2-hydroxyphenyl)-10-(4-hydroxybenzyl)-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2b***. Yield 96 %, mp 197-198 ºC. IR (KBr) ν cm$^{-1}$: 3460, 3417, 3390, and 3290, 1628. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ: 2.51 (br.s, 2H, $^+NH_2$), 1.88 (d.d, 1H, $^2J$ 9.0 Hz, $^3J$ 1.5 Hz, H-13), 2.13 (m, 1H, H-13), 2.58 (m, 1H, H-10), 2.69 (m, 1H, H-11), 2.78 (m, 1H, H-1), 4.00 (m, 2H, C$H_2$Ar), 6.70-7.11 (m, 16H, H arom), 7.07 (s,1H, N=CH),8.84 (c, 1H, OH), 12.10 (br. s, 1H, OH). MS, *m/z*: 493 $[M+H]^+$. Found (%): C, 75.63; H, 5.89; N, 5.60. Calc. for $C_{31}H_{28}N_2O_4$ (%): C, 75.59; H, 5.73; N, 5.69.

*9-[(2-Hydroxybenzylidene)amino]-11-(2-hydroxyphenyl)-10,13-diphenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2c***. Yield 27 %, mp 178-180 ºC. IR (KBr) ν cm$^{-1}$: 3460, 3390, 1626. $^1$H NMR (400 MHz, $CDCl_3$, TMS) δ ppm: 2.20 (br. s, 1H, NH), 3.77 (d, 1H, $^3J$ 9.05 Hz, H-10), 4.23 (d, 1H, $^3J$ 1.5 Hz, H-13), 4.32 (d, 1H, $^3J$ 9.0 Hz, H-11), 4.62 (d, 1H, $^3J$ 1.5Hz, H-1), 6.20-7.49 (m, 22H, H arom), 7.74 (s,1H, N=CH), 12.48 (br.s, 1H, OH). MS, *m/z*: 539 $[M+H]^+$. Found (%): C, 80.38; H, 5.38; N, 5.03. $C_{36}H_{30}N_2O_3$. Calculated, %: C, 80.30; H, 5.58; N, 5.20.

*9-[(2-Nitrobenzylidene)amino]-11-(2-hydroxyphenyl)-10,13-diphenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2d***. Yield 45 %, mp 255-257 ºC. IR (KBr) ν cm$^{-1}$: 3299, 3190, 1629, 1523, 1352. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ ppm: 2.70 (br.s, 2H, $^+NH_2$), 4.32 (d, 2H, $^3J$ 10.8Hz, H-10 and H-13), 5.15 (d, 2H, $^3J$ 10.8 Hz, H-11 and H-1), 6.93-7.81 (m, 22H, H arom), 7.91(s,1H, N=CH). MS, *m/z*: 568 $[M+H]^+$. Found (%): C, 76.07; H, 5.52; N, 7.20. $C_{36}H_{30}N_3O_4$. Calculated, %: C, 76.19; H, 5.30; N, 7.40.

*9-[(3-Nitrobenzylidene)amino]-11-(2-hydroxyphenyl)-10,13-diphenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2e***. Yield 48 %, mp 215-217 ºC. IR (KBr) ν cm$^{-1}$: 3422, 3310, 1626, 1528, 1349. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ ppm: 2.02 (br.s, 2H, $^+NH_2$ ), 4.05 (d, 2H, $^3J$ 10.2 Hz, H-10 and H-13), 4.53 (d, 2H, $^3J$ 10.2 Hz, H-11 and H-1), 6.88-7.47 (m, 19H, H arom), 7.86 (d, 1H,$^3J$ 7.6 Hz, H arom - *ortho* to nitro group), 8.12 (s, 1H, H arom – *ortho* to nitro group), 8.15 (s, 1H, N=CH). MS, *m/z*: 568 $[M+H]^+$. Found (%): C, 76.31; H, 5.22; N, 7.50.$C_{36}H_{30}N_3O_4$. Calculated, %: C, 76.19; H, 5.30; N, 7.40.

*9-[(4-Nitrobenzylidene)amino]-11-(2-hydroxyphenyl)-10,13-diphenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2f***. Yield 41 %, mp 241-243 ºC. IR (KBr) ν cm$^{-1}$: 3439, 3335, 1623, 1611, 1520, 1348. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ ppm: 2.12 (br.s, 2H, $^+NH_2$), 4.01 (d, 2H, $^3J$ 10.6 Hz, H-10 and H-13), 4.56 (d, 2H, $^3J$ 10.6 Hz, H-11 and H-1), 6.92-7.98 (m, 23H, H arom + N=CH). MS, *m/z*: 568 $[M+H]^+$. Found (%): C, 76.25; H, 5.48; N, 7.31. $C_{36}H_{30}N_3O_4$. Calculated, %: C, 76.19; H, 5.30; N, 7.40.

*9-[(4-(N,N-Dimethylamino)benzylidene)amino]-11-(2-hydroxyphenyl)-10,13-diphenyl-8-oxa-12-azatricyclo[7.3.1.0$^{2,7}$]trideca-2(7),3,5-triene,* ***2g***. Yield 51 %, mp 234-236 °C. IR (KBr) ν cm$^{-1}$: 3402, 3297, 1628. $^1$H NMR (400 MHz, $(CD_3)_2SO$, TMS) δ ppm: 2.13 (c, 6H, $NCH_3$), 2.83 and 3.11 (both br.s, 1H each, $^+NH_2$), 3.84 (d, 1H, $^3J$ 12.0 Hz, H-10), 4.15(d, 1H, $^3J$ 1.2 Hz, H-13), 4.32 (d, 1H, $^3J$ 12.0 Hz, H-11), 4.63 (d, 1H, $^3J$ 1.2 Hz, H-1), 6.18-7.55 (m, 22H, H arom), 7.77 (s, 1H, N=CH). MS, *m/z*: 566 $[M+H]^+$. Found (%): C, 80.89; H, 6.59; N, 7.26. $C_{38}H_{36}N_3O_2$. Calculated, %: C, 80.71; H, 6.37; N, 7.43.

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