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SYNTHESIS OF 2-OXA-6-AZA-3,4-BENZOBICYCLO-[3.3.1^{1,5}]NONANE FROM DIBENZYL KETONE, SALICYLALDEHYDE, AND AMMONIA

A. T. Soldatenkov[1]*, Truong Hong Hieu[1], Le Tuan Anh[2],
N. M. Kolyadina[1], and S. A. Soldatova[1]

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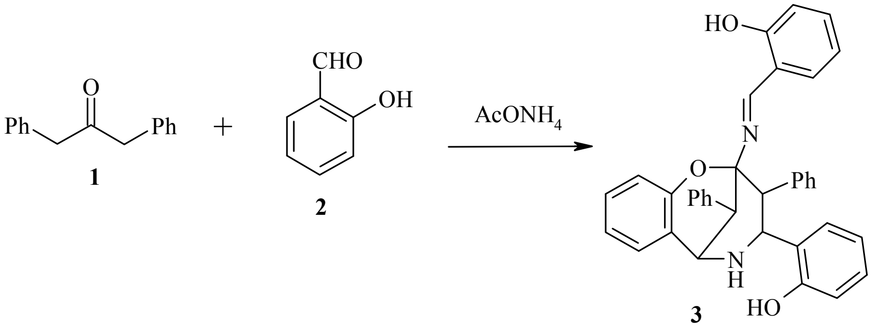
The Petrenko-Kritchenko reaction has been successfully used in the synthesis of substituted piperidin-4-ones [1-5] or their annelated derivatives [6, 7] but its potential has far from fully been utilised. Continuing our investigation into broadening the boundaries of the use of this method for the preparation of nitrogen heterocycles containing a piperidine fragment, we have studied a cascade, triple component condensation of the 1,3-dibenzyl ketone (**1**) with a considerable excess of salicylaldehyde **2** and ammonia. We propose that the piperidone intermediate arising in the above scheme [5] can further react with the excess amount of aldehyde and ammonia to give a more complex structured products. In fact, carrying out the condensation with a **1**-**2**-ammonium acetate ratio of 1:3:5 (~ 20ºC, 96 h, using alcohol in the presence of acetic acid) gave rise to an unexpected cascade formation of the 2-oxa-6-azabicyclononane **3** which can be separated from the mixture by crystallization in 27% yield. Its structure was proved unambiguously from ^{1}H NMR data, chromato-mass spectrometry, and X-ray structural analysis. Formation of the oxazocine derivative **3** is evidently preceded by reaction of the intermediate piperidone and ammonia to give an unstable geminal γ-aminol which is then stabilized *via* two reactions, *viz.* an intramolecular etherification with one of the *ortho*-hydroxyphenyl substituents and an intermolecular imination with excess aldehyde.



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* To whom correspondence should be addressed, e-mail: soldatenkovat@yandex.ru.

[1] Peoples' Friendship University of Russia, Moscow 117198, Russia.
[2] Vietnam State University, Hanoi Science University, Vietnam; e-mail: lta@vnu.edu.vn.

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IR spectra were recorded on an Infralum FT-801 spectrometer for KBr tablets. ^{1}H NMR spectra were taken on a Bruker WP-400 (400 MHz) spectrometer using $CDCl_3$ and with the residual protons of the deuterated solvent as internal standard. The analysis of the reaction mixture and purity of the separated compound **3** was performed on an Agilent 1100 liquid chromatograph with DAD, ELSD Sedex 75 detectors in combination with an Agilent LC/MSD VL mass spectrometer using electrospray ionization. X-ray analysis was performed by the direct method on a Bruker SMART 100 CCD diffractometer (MoKα radiation, graphite monochromator, Θ- and ω-scanning). The X-ray structural data was deposited in the Cambridge structural database (reference CCDC 800614).

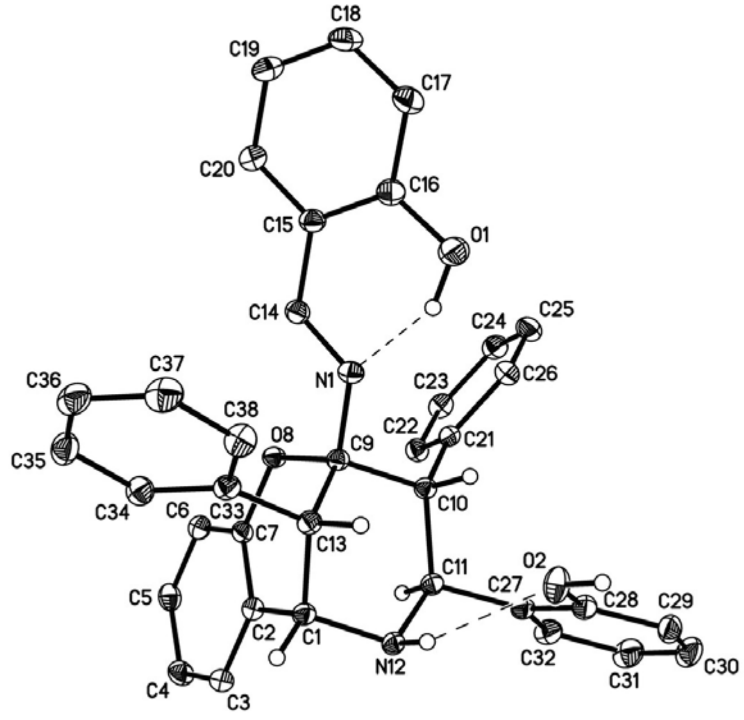

Fig 1. Molecule of compound **3**.

7-(2-Hydroxyphenyl)-1-(2-hydroxyphenylmethyleneimino)-8,9-diphenyl-2-oxa-6-aza-3,4-benzobicyclo- [3.3.1^{1,5}]nonane (3). A solution of ketone **1** (2.1 g, 10 mmol), salicylaldehyde **2** (6.0 g, 30 mmol), and ammonium acetate (4.0 g, 52 mmol) in alcohol (40 ml) was stirred at ~ 20ºC for 96 h. The precipitate formed was filtered off, washed with alcohol (10 ml) and ether (10 ml), and recrystallized from alcohol to give compound **3** (1.48 g, 27%) as colorless crystals with mp 178-180ºC. IR spectrum, ν, cm^{-1}: 3460 (OH) and 3390 (NH), 1626 (N=CH). ^{1}H NMR spectrum, δ, ppm (J, Hz): 2.20 (1H, br. s, NH); 3.77 (1H, d, J = 9.0, H-8); 4.23 (1H, d, J = 1.5, H-9); 4.32 (1H, d, J = 9.0, H-7); 4.62 (1H, d, J = 1.5, H-5); 6.20-7.49 (22H, m, H arom); 7.74 (1H, s, N=CH); 12.48 (1H, br. s, OH). Mass spectrum, m/z (I_{rel}, %): 538 [M]$^+$. 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.

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