ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 12, pp. 1843–1847. © Pleiades Publishing, Ltd., 2010.
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Synthesis of New Benzo[*c*]phenanthridine Derivatives

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Received December 2, 2009

Abstract—Three-component condensation of naphthalen-1-amine with triethyl orthoformate and dimedone or cyclopentane-1,3-dione, as well as the reaction of naphthalen-1-amine with 2-acetyl-5,5-dimethylcyclohexane-1,3-dione, gave the corresponding 2-[1-(α-naphthylamino)alkylidene]cycloalkane-1,3-diones which underwent intramolecular cyclization to 7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-one derivatives on heating in polyphosphoric acid. 9,9-Dimethyl-7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-one was reduced to 9,9-dimethyl-7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-ol with sodium tetrahydridoborate.

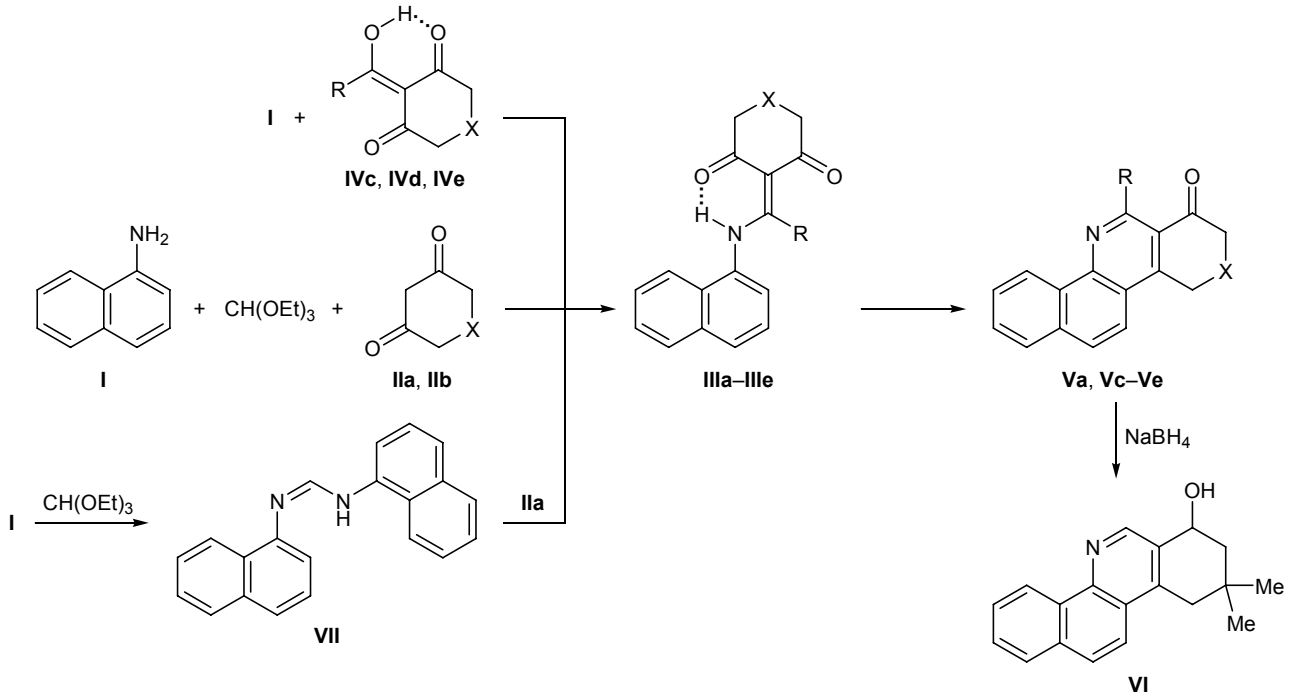
DOI: 10.1134/S1070428010120134

Synthesis of new benzo[*c*]phenanthridine derivatives like **V** and **VI** attracts interest, taking into account that such compounds exhibit a broad spectrum of biological activity [1, 2]. Among naturally occurring analogs, benzo[*c*]phenanthridine alkaloids are known [3, 4]. The synthesis of tetrahydrobenzo[*c*]phenanthridine derivatives **Vd** and **Ve** via reaction of naphthalen-1-amine (**I**) with 2-acylcyclohexane-1,3-diones **IVd** and **IVe** and subsequent cyclization of enamino diketones **IIId** and **IIIe** in polyphosphoric acid was described previously [5] (Scheme 1). Martinez et al. [6] synthesized compound **Va** in three steps. The reaction of naphthalen-1-amine (**I**) with triethyl orthoformate gave the corresponding formamidine **VII** which reacted with dimedone (**IIa**) to produce imino ketoenol **IIIa**, and the latter was subjected to cyclization on heating in polyphosphoric acid.

In the present work tetracyclic compound **Va** was synthesized in two steps. Three-component condensation of naphthalen-1-amine (**I**) with triethyl orthoformate and dimedone (**IIa**) in the presence of acetic acid afforded enamino diketone **IIIa** which was then heated in polyphosphoric acid to obtain the target product, benzo[*c*]phenanthridine derivative **Va** (Scheme 1). Likewise, three-component reaction of naphthalen-1-amine (**I**) with triethyl orthoformate and cyclopentane-1,3-dione (**IIb**) gave enamino diketone **IIIb**. However, compound **IIIb** failed to undergo intramolecular cyclization on heating in polyphosphoric acid at 170°C, whereas a complex mixture of products was formed at a higher temperature.

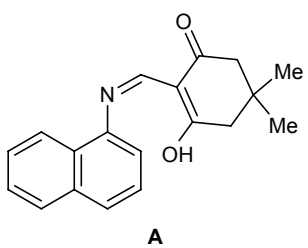
The structure of the isolated compounds was confirmed by their elemental analyses and NMR, IR, and mass spectra. All compounds displayed the molecular ion peaks in the mass spectra. The structure of the enamino diketone fragment in **IIIa** followed from the presence of signals from two carbonyl carbon atoms in the ^{13}C NMR spectrum (δ_C 196.10, 200.18 ppm). *cis–trans* Isomerism with respect to the exocyclic double bond is not possible, for the substituents on the C^2 atom are similar. The *s-cis* orientation of the carbonyl group relative to the double bond is fixed by the cyclohexane ring. The ^1H NMR spectrum of **IIIa** contained two downfield doublets at δ 13.66 and 8.68 ppm. The first of these corresponds to the NH proton, and the second, to the olefinic proton coupled with the NH proton. The coupling constant ^3J is equal to 12.5 Hz, indicating *anti* orientation of these protons about the C–N bond. On the whole, the ^1H NMR spectrum of **IIIa** corresponds to the *cis-s-cis* structure of the enamino carbonyl system [7, 8]. Obviously, the formation of intramolecular hydrogen bond is the main factor stabilizing the antiplanar conformation which appears due to rotation about the C–N bond in molecules **IIIa**–**IIIe**. In keeping with published data, *cis-s-cis* conformation of enamino carbonyl system is more stable than imino ketone or imino enol [7, 9]. The compound obtained in [6] was assigned imino enol structure **A** with *Z* configuration [10] of substituents about the double C=N bond. Obviously, this structure excludes formation of intramolecular hydrogen bond between the enol proton and nitrogen atom, whereas the chemical shift of the hydroxy proton (δ 11.3 ppm)

Scheme 1.

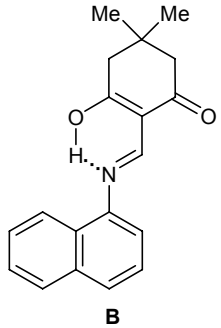


X = CMe_2 (**a**, **c**, **e**), bond (**b**), CH_2 (**d**); R = H (**a**, **b**), Me (**c**), Et (**d**), Ph (**e**).

suggests that such hydrogen bond does exist. In terms of *s-cis–s-trans* isomerism for a system of two conjugated double bonds [7], structure **A** is characterized by *cis-s-cis* configuration. In addition, *cis-s-trans* configuration is possible, but it also excludes intramolecular hydrogen bonding. The formation of intramolecular hydrogen bond could be expected for the *E* isomer; however, in this case *trans-s-cis* imino enol structure **B** and the enamino ketone structure of **IIIa** shown in Scheme 1 are tautomeric, and they cannot be distinguished in the NMR spectra. The transformation from one tautomer to another involves proton transfer from the nitrogen atom in the enamino tautomer to the ketone carbonyl oxygen atom and *vice versa*, from the enol oxygen atom to the imino nitrogen atom. The energy barrier to such transition is low. Possible *trans-s-trans* imino ketoenol structure also excludes formation of intramolecular hydrogen bond. Although there are some differences in the ^{1}H NMR spectra of samples of **IIIa** isolated in the present work and in [6], they correspond most probably to the same compound, for transformation of any of the above isomeric structure into another form could occur via intra- or intermolecular proton exchange [7]. Thus compound **IIIa** may be presumed to exist in solution an equilibrium mixture of tautomers, the enamino ketone structure prevailing.



A



B

The ^{1}H NMR spectrum of enamino diketone **IIIb** contained a downfield broadened singlet at δ 12.66 ppm, which was assigned to the NH proton involved in intramolecular hydrogen bond with the carbonyl oxygen atom.

Naphthalen-1-amine (**I**) reacted with triketone **IVc** to give enamino diketone **IIIc** which showed in the ^{1}H NMR spectrum a signal at δ 15.16 ppm due to the NH proton (H-bonded). The presence in the ^{13}C NMR spectra of enamino diketones **IIId** and **IIIe** of signals from two carbonyl carbon atoms (δ_C 196.54 and 201.36 ppm for **IIId** and δ_C 195.15 and 200.55 ppm for **IIIe**) indicated that these compounds exist as enamino diketone tautomers.

In the ^{1}H NMR spectra of compounds **Va** and **Vc–Ve** a one-proton singlet was observed in a weak field

(δ 9.35–9.45 ppm, 6-H). The reduction of ketone **Va** with sodium tetrahydridoborate gave alcohol **VI** whose spectral parameters and elemental composition were consistent with the assumed structure. The coupling constants for the 7-H proton and protons in the neighboring methylene group (J = 5.0, 12.0 Hz) indicated pseudoaxial orientation of 7-H and hence pseudoequatorial orientation of the hydroxy group in the cyclohexene ring occurring in a *half-chair* conformation.

It should also be noted that the ^{1}H NMR and mass spectra given in [6] for the reaction product of ketone **Va** with ethylene glycol coincided with the corresponding spectral data for the initial ketone rather than for the assumed cyclic acetal.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using ethyl acetate as eluent; spots were visualized under UV light or by treatment with iodine vapor. The melting points were determined on a Boetius melting point apparatus. The IR spectra were recorded in KBr on a UR-20 instrument. The mass spectra (electron impact, 70 eV) were obtained on a Varian MAT-311 mass spectrometer with direct sample admission into the ion source. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC-200 instrument from solutions in $CDCl_3$; the ^{13}C NMR spectra were recorded with decoupling from protons.

5,5-Dimethyl-2-[(naphthalen-1-ylamino)methylidene]cyclohexane-1,3-dione (IIIa). A mixture of 1.43 g (10 mmol) of napthalen-1-amine (**I**), 1.4 g (10 mmol) of 5,5-dimethylcyclohexane-1,3-dione (**IIa,** dimedone), 3 ml of of triethyl orthoformate, and 2 ml of acetic acid was heated for 1.5 h under reflux. Volatile compounds were removed under reduced pressure, and the residue was crystallized from ethyl acetate. Yield 2.50 g (85%), mp 148–150°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3450 (N–H); 1677, 1605, 1580 (C=O, C=C). ^{1}H NMR spectrum, δ, ppm: 1.08 s (6H, CH_3), 2.39 s (2H, CH_2), 2.46 s (2H, CH_2), 7.30–7.70 m (5H, H_{arom}), 7.79 d (1H, H_{arom}, J = 7 Hz), 8.00 d (1H, H_{arom}, J = 7 Hz), 8.68 d (1H, CH=, J = 12 Hz), 13.66 d (1H, NH, J = 12 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.57 (CH_3), 31.16 (C^3), 51.26 and 51.53 (C^2, C^4), 109.53 (C^6), 114.07 (CH), 120.44 (CH), 125.23 (C), 125.60 (CH), 126.88 (CH), 127.29 (CH), 128.57 (CH), 134.02 (C), 134.60 (C), 151.75 (CH), 196.10 (CO), 200.18 (CO). Mass spectrum, m/z: 293 $[M]^+$, 275 $[M - H_2O]$. Found, %: C 77.61; H 6.29; N 4.83. $C_{19}H_{19}NO_2$. Calculated, %: C 77.68; H 6.20; N 4.77.

2-[(Naphthalen-1-ylamino)methylidene]cyclopentane-1,3-dione (IIIb). A mixture of 1.43 g (10 mmol) of naphthalen-1-amine (**I**), 0.98 g (10 mmol) of cyclopentane-1,3-dione (**IIb**), 3 ml of triethyl orthoformate, and 2 ml of glacial acetic acid was heated for 1.5 h under reflux. Volatile compounds were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (Silicagel L, 100–160 μm) using ethyl acetate–hexane (1:3, 1:2, 1:1) as eluent. Yield 1.53 g (61%), mp 164–166°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3440 (NH); 1700, 1635 (C=O); 1625, 1615, 1598 (C=C); 1580, 1520, 1490. ^{1}H NMR spectrum, δ, ppm: 2.32 m (4H, CH_2), 7.30 m (2H, H_{arom}), 7.48 m (2H, H_{arom}), 7.62 d (1H, J = 8 Hz), 7.76 d (1H, J = 8 Hz), 7.86 d (1H, J = 8 Hz), 8.16 s (1H), 12.66 br.s (NH). Mass spectrum: m/z 256 $[M]^+$. Found, %: C 76.41; H 5.30; N 5.63. $C_{16}H_{13}NO_2$. Calculated, %: C 76.48; H 5.21; N 5.57.

5,5-Dimethyl-2-[1-(naphthalen-1-ylamino)ethylidene]cyclohexane-1,3-dione (IIIc). A mixture of 1.82 g (10 mmol) of 2-acetyl-5,5-dimethylcyclohexane-1,3-dione (**IVa**) and 1.43 g (10 mmol) of naphthalen-1-amine in 60 ml of toluene was heated for 2 h under reflux in a flask equipped with a Dean–Stark trap. The solvent was distilled off, and the residue was crystallized from 20 ml of ethyl acetate. Yield 2.70 g (88%), mp 149–151°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3440 (N–H); 1645, 1630, 1580 (C=C, C=O). ^{1}H NMR spectrum, δ, ppm: 1.12 s (6H, CH_3), 2.46 s (5H, CH_2, CH_3), 2.58 s (CH_2), 7.30 m (1H), 7.56 m (3H), 7.88 m (3H), 15.16 br.s (NH). Mass spectrum, m/z: 307 $[M]^+$, 279 $[M - CO]$. Found, %: C 78.21; H 6.99; N 4.64. $C_{20}H_{21}NO_2$. Calculated, %: C 78.13; H 6.88; N 4.56.

Compounds **IIId** and **IIIe** were synthesized in a similar way.

2-[1-(Naphthalen-1-ylamino)propylidene]cyclohexane-1,3-dione (IIId) was synthesized from 1.68 g (10 mmol) of 2-(1-oxopropyl)cyclohexane-1,3-dione (**IVd**) and 1.43 g (10 mmol) of naphthalen-1-amine. Yield 2.67 g (91%), mp 172–174°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3440 (N–H); 1650, 1570, 1550 (C=C, C=O). ^{1}H NMR spectrum, δ, ppm: 1.04 t (3H, CH_3, J = 7 Hz), 2.00 q (2H, CH_2, J = 7 Hz), 2.62 m (4H, CH_2), 2.86 q (2H, J = 7 Hz), 7.30–7.90 m (7H, H_{arom}), 15.29 br.s (NH). ^{13}C NMR spectrum, δ_C, ppm: 13.32 (CH_3), 19.35 (CH_2), 24.74 (CH_2), 38.88 (CH_2),

40.10 (CH_2), 108.38 (C^6), 122.47 (CH), 124.09 (CH), 125.13 (CH), 126.92 (CH), 127.41 (CH), 128.35 (CH), 128.59 (CH), 129.78 (C), 132.85 (C), 134.16 (C), 179.72 (C), 196.54 (CO), 201.36 (CO). Mass spectrum, *m*/*z*: 293 $[M]^+$, 265 [*M* – CO]. Found, %: C 77.63; H 6.24; N 4.85. $C_{19}H_{19}NO_2$. Calculated, %: C 77.68; H 6.20; N 4.77.

5,5-Dimethyl-2-[α-(naphthalen-1-ylamino)benzylidene]cyclohexane-1,3-dione (IIIe) was synthesized from 2.44 g (10 mmol) of 2-benzoylcyclohexane-1,3-dione (**IVe**) and 1.43 g (10 mmol) of naphthalen-1-amine. Yield 3.33 g (90%), mp 201–202°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 3440 (N–H); 1658, 1580, 1536 (C=C, C=O). ^{1}H NMR spectrum, δ, ppm: 1.16 s (6H, CH_3), 2.38 s (2H, CH_2), 2.64 s (2H, CH_2), 6.74 d (1H, H_{arom}, *J* = 7 Hz), 6.90–7.70 m (9H, H_{arom}), 8.10 d (1H, H_{arom}, *J* = 7 Hz), 15.05 br.s (NH). ^{13}C NMR spectrum, δ_C, ppm: 28.47 (CH_3), 30.30 (C^3), 52.37 (CH_2), 53.24 (CH_2), 108.83 (C^6), 122.14 (CH), 123.60 (C), 124.61 (CH), 126.54 CH), 127.17 (CH), 127.31 (C), 127.80 (CH), 128.27 (CH), 128.74 (CH), 129.41 (CH), 133.14 (CH), 133.65 (CH), 134.06 (C), 171.06 (C), 195.15 (CO), 200.55 (CO). Mass spectrum, *m*/*z*: 369 $[M]^+$, 341 [*M* – CO]. Found, %: C 81.21; H 6.20; N 3.86. $C_{25}H_{23}NO_2$. Calculated, %: C 81.27; H 6.27; N 3.79.

9,9-Dimethyl-7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-one (Va). A mixture of 1.46 g (5 mmol) of enamino diketone **IIIa** and 40 g of polyphosphoric acid (prepared from 134 g of P_2O_5 and 65 ml of H_3PO_4) was stirred for 1.5 h at 170°C. The mixture was cooled, carefully diluted with 50 ml of ice water, and neutralized with solid potassium hydroxide to pH 6.0. The precipitate was filtered off, washed with water, and dried in air. Yield 1.24 g (90%), mp 196–197°C (from ethyl acetate). IR spectrum, ν, cm^{-1}: 1620 (C=N), 1572, 1513. ^{1}H NMR spectrum, δ, ppm: 1.22 s (6H, CH_3), 2.50 s (CH_2), 3.14 s (CH_2), 7.70–7.96 m (5H), 9.34 m (1H), 9.45 s (1H, 6-H). ^{13}C NMR spectrum, δ_C, ppm: 28.56 (CH_3), 33.13 (C^9), 38.95 (C^{10}), 51.59 (C^8), 120.72 (CH), 123.94 (C), 124.23 (C), 125.60 (CH), 127.32 (CH), 127.37 (CH), 127.65 (CH), 129.11 (CH), 131.52 (C), 134.08 (C), 146.90 (CH), 148.32 (C), 197.70 (CO). Mass spectrum, *m*/*z*: 275 $[M]^+$, 260 [*M* – CH_3], 247 [*M* – CO]. Found, %: C 82.79; H 6.29; N 5.15. $C_{19}H_{17}NO$. Calculated, %: C 82.87; H 6.23; N 5.09.

Compounds **Vc**–**Ve** were synthesized in a similar way.

6,9,9-Trimethyl-7,8,9,10-tetrahydrobenzo[*c*]-phenanthridin-7-one (Vc) was synthesized from 1.54 g (5 mmol) of enamino diketone **IIIc**. Yield 1.28 g (88%), mp 145–147°C (from EtOH). IR spectrum, ν, cm^{-1}: 1678 (C=O); 1628, 1570 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.15 s (6H, CH_3), 2.54 s (CH_2), 3.07 s (CH_3), 3.18 s (CH_2), 7.64–7.92 m (5H), 9.35 m (1H, 12-H). Mass spectrum, *m*/*z*: 289 $[M]^+$, 274 [*M* – CH_3], 261 [*M* – CO]. Found, %: C 83.09; H 6.71; N 4.91. $C_{20}H_{19}NO$. Calculated, %: C 83.01; H 6.62; N 4.84.

6-Ethyl-7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-one (Vd) was synthesized from 1.46 g (5 mmol) of enamino diketone **IIId**. Yield 1.22 g (89%), mp 170–172°C (from EtOAc). IR spectrum, ν cm^{-1}: 1680 (C=O); 1562, 1509 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.46 t (3H, CH_3, *J* = 7 Hz), 2.22 q (2H, CH_2, *J* = 6 Hz), 2.72 t (2H, CH_2, *J* = 6 Hz), 3.34 t (2H, CH_2, *J* = 6 Hz), 3.44 q (2H, CH_2, *J* = 7 Hz), 7.76 m (5H, H_{arom}), 9.39 m (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 13.03 (CH_3), 21.97 (CH_2), 26.19 (CH_2), 31.89 (CH_2), 40.16 (CH_2), 120.74 (CH), 122.03 (C), 124.65 (C), 125.60 (CH), 127.01 (CH), 127.15 (CH), 127.45 (CH), 128.80 (CH), 131.33 (C), 134.16 (C), 146.12 (C), 151.31 (C), 162.47 (C), 199.13 (CO). Mass spectrum: *m*/*z* 275 $[M]^+$. Found, %: C 82.80; H 6.31; N 5.17. $C_{19}H_{17}NO$. Calculated, %: C 82.87; H 6.23; N 5.09.

9,9-Dimethyl-6-phenyl-7,8,9,10-tetrahydrobenzo-[*c*]phenanthridin-7-one (Ve) was synthesized from 1.80 g (5 mmol) of enamino diketone **IIIe**. Yield 1.54 g (88%), mp 246– 247°C (from EtOAc). IR spectrum, ν, cm^{-1}: 1678 (C=O); 1570, 1552, 1500 (C=C, C=N). ^{1}H NMR spectrum, δ, ppm: 1.22 s (6H, CH_3), 2.62 s (2H, CH_2), 3.34 s (2H, CH_2), 7.40–8.00 m (10H, H_{arom}), 9.36 m (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 28.64 (CH_3), 33.36 (C^9), 40.12 (C^{10}), 53.11 (C^8), 120.64 (CH), 122.99 (C), 124.72 (C), 125.80 (CH), 127.21 (CH), 127.48 (CH), 127.77 (CH), 127.98 (CH), 128.09 (CH), 128.58 (C), 129.10 (CH), 131.46 (C), 134.22 (CH), 142.11 (C), 146.46 (C), 149.98 (C), 157.76 (C), 198.23 (CO). Mass spectrum: *m*/*z* 351 $[M]^+$. Found, %: C 85.39; H 6.11; N 4.05. $C_{25}H_{21}NO$. Calculated, %: C 85.44; H 6.02; N 3.99.

9,9-Dimethyl-7,8,9,10-tetrahydrobenzo[*c*]phenanthridin-7-ol (VI). A mixture of 0.3 g of ketone **Va**, 50 ml of propan-2-ol, 5 ml of water, and 0.5 g of $NaBH_4$ was stirred for 3 h and was then kept for 20 h at room temperature. The solvent was distilled off, and the residue was treated with 50 ml of ethyl acetate and 50 ml of water. The organic phase was separated and dried over magnesium sulfate, the solvent was distilled off, and the residue was crystallized from ethyl acetate.

Yield 0.22 g (73%), mp 176–178°C (from EtOAc). IR spectrum, ν, cm^{-1}: 1578, 1515 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 0.90 s (3H, CH_3), 1.04 s (3H, CH_3), 1.46 t (1H, 8-H_{ax}, J = 12 Hz), 2.02 d.d (1H, 8-H_{eq}, J = 5, 12 Hz), 2.47 and 2.81 (1H each, 10-H, *AB* system, J_{AB} = 17 Hz), 4.98 d.d (1H, 7-H_{ax}, J = 5, 12 Hz), 7.60–7.98 m (5H, H_{arom}), 9.15 s (1H, 6-H), 9.24 d (12-H, J = 8 Hz). Mass spectrum, m/z: 277 $[M]^+$, 276 [M – H], 260 [M – OH], 244, 221. Found, %: C 82.20; H 7.00; N 5.11. $C_{19}H_{19}NO$. Calculated, %: C 82.28; H 6.90; N 5.05.

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