ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 6, pp. 886–889. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © V.O. Topuzyan, A.R. Manvelyan, V.V. Grigoryan, R.A. Tamazyan, A.G. Aivazyan, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 6, pp. 901–903.

Derivatives of α,β-Dehydro Amino Acids: VI.* Reaction of 4-Benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one with Piperidin-2-ylmethanamine

V. O. Topuzyan, A. R. Manvelyan, V. V. Grigoryan, R. A. Tamazyan, and A. G. Aivazyan

Mndzhoyan Institute of Fine Organic Chemistry, Scientific–Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, pr. Azatutyan 26, Yerevan, 375014 Armenia
e-mail: vtop@web.am

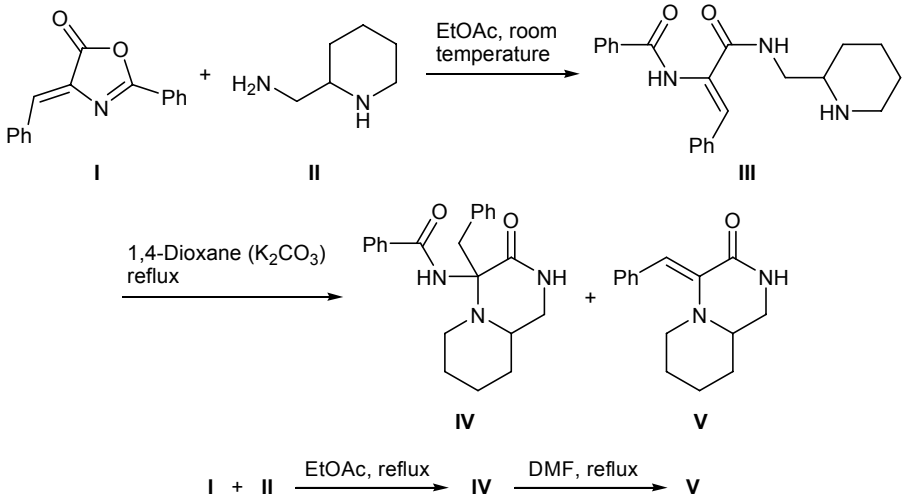
Received August 28, 2012

Abstract—4-Benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one reacts with piperidin-2-ylmethanamine to give *N*-{(*Z*)-3-oxo-3-[(piperidin-2-ylmethyl)amino]-1-phenylprop-1-en-2-yl}benzamide, *N*-(4-benzyl-3-oxooctahydro-2*N*-pyrido[1,2-*a*]pyrazin-4-yl)benzamide, or/and (*Z*)-4-benzylidenehexahydro-2*H*-pyrido[1,2-*a*]pyrazin-3(2*H*)-one, depending on the solvent, temperature, and reaction time. The latter product is formed via three-step tandem process.

DOI: 10.1134/S1070428013060146

We previously found that amino amides derived from *N*-substituted α,β-dehydro amino acids undergo intramolecular cyclization in dioxane in the presence of potassium carbonate to produce fused heterocyclic systems [1, 2]. In continuation of these studies, we now report on the reaction of 4-benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one (**I**) with piperidin-2-ylmethanamine (**II**). The reaction in ethyl acetate at room temperature gave *N*-{(Z)-3-oxo-1-phenyl-3-[(piperidin-2-ylmethyl)amino]prop-1-en-2-yl}benzamide (**III**), whereas *N*-(4-benzyl-3-oxooctahydro-2*H*-pyrido-[1,2-*a*]pyrazin-4-yl)benzamide (**IV**) was obtained on heating under reflux (Scheme 1). Compound **IV** was also formed when amide **III** was heated in dioxane both in the presence and in the absence of K_2CO_3. However, in these cases, (*Z*)-4-benzylidenehexahydro-2*H*-pyrido[1,2-*a*]pyrazin-3(4*H*)-one (**V**) was isolated from the reaction mixture in addition to benzamide **IV**.

Scheme 1.

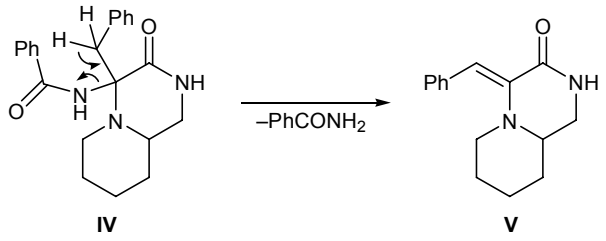


* For communication V, see [1].

We examined how the solvent nature affects the intramolecular cyclization of **III** (see table). Protic solvents (methanol) hampered the reaction, whereas ethyl acetate and dioxane ensured formation of **IV** in good yield. However, prolonged heating of the reaction mixture in boiling dioxane favored formation of compound **V**. The latter was isolated as the major product when the reaction was carried out in acetonitrile or DMF. In DMF, 85% of **V** was obtained in 1 h. These findings allowed us to conclude that unsaturated compound **V** is formed from dehydro amino acid derivative **III** through intermediate amide **IV**. This conclusion was confirmed by the transformation of amide **IV** into compound **V** on heating in boiling DMF for 1.5 h (yield 75%).

We also tried to obtain fused heterocyclic compound **V** directly from 4-benzylidene-2-phenyloxazol-5(4*H*)-one (**I**) and amine **II**. In fact, the reaction in DMF afforded pyrido[1,2-*a*]pyrazin-3(2*H*)-one **V**. Obviously, the latter is formed via three-step tandem process, the last step of which is elimination of benzamide molecule from compound **IV** (Scheme 2).

Scheme 2.



IV **V**

According to the X-ray diffraction data, the exocyclic double C=C bond in molecule **V** has *Z* configuration (Fig. 1). Compound **V** was also found to be a racemic mixture of *S*- and *R*-stereoisomers linked to dimers by hydrogen bonds $N^8–H^8\cdots O^{10i}$, the O···H distance being 2.880(3) Å (Fig. 2). The piperidine ring in molecule **V** adopts a regular *chair* conformation.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Varian Mercury 300 instrument. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates using toluene–hexane–ethanol (1 : 1 : 1) as eluent; spots were visualized under UV light or by treatment with iodine vapor.

The X-ray diffraction data for a single crystal of **V** were acquired on an Enraf–Nonius CAD-4 automatic diffractometer. The unit cell parameters were determined at room temperature and were refined from 22 reflections in the range $9.4 < \theta < 11.2$: monoclinic crystal system; $a = 6.3076(3)$, $b = 13.4440(2)$, $c = 15.4067(3)$ Å; $\beta = 95.33(3)°$; $V = 1300.8(5)$ Å^3; space group $P2_1/n$ ($Z = 4$). Total of 4078 reflection intensities were measured at $0 \le h \le 8$, $0 \le k \le 18$, $-21 \le l \le 21$, $\theta_{max} = 30$ (MoK_α irradiation, graphite monochromator). All calculations were carried out using SHELXTL software package [3]. Averaging of symmetry-equiv-

Effect of solvent on the cyclization of *N*-{(1*Z*)-3-oxo-1-phenyl-3-[(piperidin-2-ylmethyl)amino]prop-1-en-2-yl}-benzamide (**III**)

Solvent	Reaction time, h	Temperature, °C	Yield, %	
			IV	**V**
Methanol	8	65	Traces[a]	0
Ethyl acetate	29	77	65	0
Ethyl acetate	34	77	76	0
Chloroform	34	61	Mixture **IV**/**V**[a]	
1,4-Dioxane	3	101	62.0	Traces[a]
1,4-Dioxane	19	101	Traces[a]	31.0
1,4-Dioxane	41	101	0	71.6
Acetonitrile	29	82	0	64.5
DMF	1	145	0	85.7

[a] According to the TLC data.

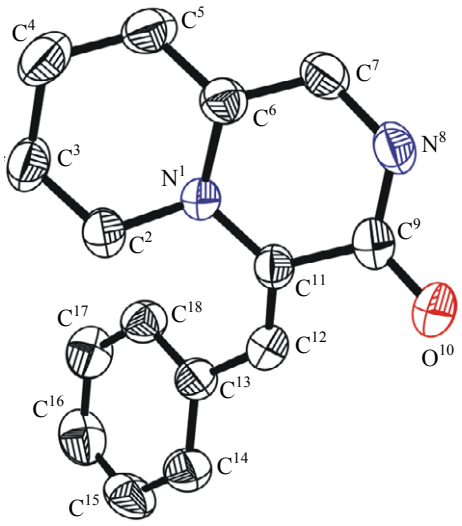


Fig. 1. Structure of the molecule of (4*Z*,9a*R*)-4-benzylidene-hexahydro-2*H*-pyrido[1,2-*a*]pyrazin-3(4*H*)-one (**V**) according to the X-ray diffraction data (arbitrary atom numbering).

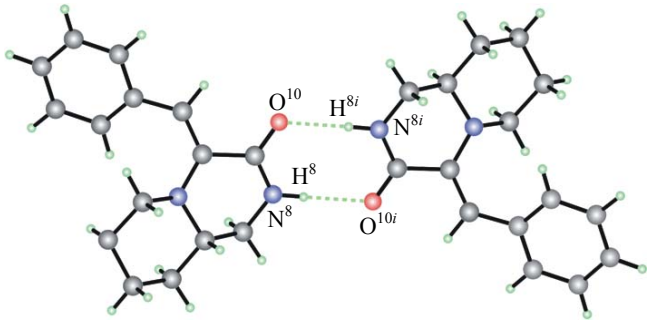


Fig. 2. Hydrogen-bonded dimer formed by *R*- and *S*-stereoisomeric molecules of (*Z*)-4-benzylidenehexahydro-2*H*-pyrido[1,2-*a*]pyrazin-3(4*H*)-one (**V**) in crystal (symmetry operation *i*: –*x*, 1 – *y*, –*z*).

alent reflections left 3768 independent reflections (R_{int} = 0.028), 2160 of which were characterized by $I > 2\sigma(I)$. The structure was solved by the direct method and was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atoms. The positions of hydrogen atoms were determined by the Fourier difference syntheses and were refined in isotropic approximation. The final divergence factor was R = 0.067; goodness of fit S = 1.05. The set of crystallographic data for compound **V** (as *cif* file) was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 891800).

***N*-{(*Z*)-3-Oxo-1-phenyl-3-[(piperidin-2-ylmethyl)amino]prop-1-en-2-yl}benzamide (III).** A mixture of 1.0 g (4 mmol) of 4-benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one (**I**) [4] and 0.46 g (4 mmol) of piperidin-2-ylmethanamine (**II**) in 20 ml of ethyl acetate was stirred for 24 h at room temperature. The solid material was filtered off, washed with diethyl ether (40 ml), and dried in air. Yield 1.15 g (79%), mp 149–151°C (from ethyl acetate), R_f 0.16. IR spectrum, ν, cm^{-1}: 3284, 1655, 1650, 1640. ^{1}H NMR spectrum, δ, ppm: 1.07 m (1H, CH_2), 1.25–1.43 m (2H, CH_2), 1.64–1.47 m (2H, CH_2), 1.77 m (1H, CH_2), 2.03 br.s (1H, NH), 2.56 m (1H, CH_2), 2.64 m (1H, CH), 2.97 m (1H, CH_2), 3.03 d.d.d (1H, CH_2, J = 13.0, 7.7, 6.1 Hz), 3.21 d.d.d (1H, CH_2, J = 13.0, 5.6, 4.4 Hz), 7.13 s (1H, CH=C), 7.22–7.34 m (3H, C_6H_5), 7.57–7.42 m (5H, C_6H_5), 7.81 d.d (1H, CH_2, J = 6.1, 5.6 Hz), 8.00 m (2H, C_6H_5), 9.76 br.s (1H, N**H**COPh). Found, %: C 72.49; H 6.80; N 11.41. $C_{22}H_{25}N_3O_2$. Calculated, %: C 72.74; H 6.94; N 11.57.

***N*-(4-Benzyl-3-oxooctahydro-2*H*-pyrido[1,2-*a*]pyrazin-4-yl)benzamide (IV).** *a*. A solution of 1 g (2.76 mmol) of compound **III** in 15 ml of dioxane was heated for 3 h under reflux. The mixture was cooled, and the precipitate was filtered off, washed with 20 ml of dioxane, and dried in air. Yield 0.62 g (64%), mp 174–177°C, R_f 0.69. According to the TLC data, the filtrate contained compound **V** (R_f 0.74).

b. A solution of 1 g (4 mmol) of oxazole **I** and 0.46 g of amine **II** in 15 ml of ethyl acetate was heated for 39 h under reflux. The precipitate was filtered off, washed with 15 ml of ethyl acetate, and dried in air. Yield 0.92 g (63%). The product was identical in physicochemical characteristics to a sample obtained as described above in *a*. IR spectrum, ν, cm^{-1}: 3265, 3180, 1690, 1665. ^{1}H NMR spectrum, δ, ppm: 0.83 (1H), 1.23 (1H), and 1.40–1.73 (4H) (CH_2); 1.77 d.d (1H, CH_2, J = 11.7, 10.6 Hz), 2.25 t.d (1H, CH_2, J = 12.1, 2.3 Hz), 2.68 d.d.d (1H, CH_2, J = 11.7, 5.6, 3.4 Hz), 3.00 d (1H, CH_2, J = 12.4 Hz), 3.07 d (1H, CH_2, J = 12.4 Hz), 3.13 m (1H, CH_2), 3.31 t.t (1H, CH, J = 10.6, 2.9 Hz), 7.15–7.24 m (5H, C_6H_5), 7.34 d (1H, C_6H_5, J = 5.6 Hz), 7.50–7.38 m (3H, C_6H_5), 7.89 m (2H, C_6H_5), 8.06 s (1H, NH). Found, %: C 72.56; H 6.67; N 11.69. $C_{22}H_{25}N_3O_2$. Calculated, %: C 72.74; H 6.94; N 11.57.

(*Z*)-4-Benzylidenehexahydro-2*H*-pyrido[1,2-*a*]pyrazin-3(4*H*)-one (V). *a*. A solution of 0.5 g (1.3 mmol) of compound **III** in 5 ml of DMF was heated for 1 h under reflux. The mixture was cooled and diluted with 20 ml of water, and the precipitate was filtered off. Yield 0.28 g (85%), mp 232–235°C, R_f 0.74.

b. Amine **II**, 0.46 g (4 mmol), was added to a solution of 1.0 g (4 mmol) of oxazolone **I** in 10 ml of dimethylformamide, and the mixture was heated for 1 h under reflux. The mixture was cooled and diluted with 20 ml of water, and the precipitate was filtered off, washed with diethyl ether (30 ml), and dried in air. Yield 0.75 g (77%).

c. A solution of 0.5 g (1.3 mmol) of compound **IV** in 10 ml of dimethylformamide was heated for 1.5 h under reflux. The mixture was cooled and diluted with 50 ml of water, and the precipitate was filtered off, washed with water, and dried in air. Yield 0.25 g (75%). Samples of **V** prepared by the three methods were identical in physicochemical characteristics. IR spectrum, ν, cm^{-1}: 3170, 1665. ^{1}H NMR spectrum, δ, ppm: 1.32–1.86 m (6H, CH_2), 2.46 m and 2.39 m (2H, NCH_2), 3.23–3.11 m (2H, NCH_2), 3.32 d.t (1H, CH, J = 12.5, 3.5 Hz), 6.40 s (1H, C=CH), 7.44–7.08 m (5H, C_6H_5), 7.90 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 22.683, 24.244, 28.596, 38.942, 39.225, 39.500, 39.775, 40.058, 43.100, 50.153, 56.891,

110.425, 125.446, 127.315, 128.027, 136.463, 139.214, 163.934. Found, %: C 74.16; H 7.54; N 11.72. $C_{15}H_{18}N_2O$. Calculated, %: C 74.39; H 7.49; N 11.57.

REFERENCES

1. Topuzyan, V.O., Kazandzhyan, M.M., Tamazyan, R.A., and Aivazyan, A.G., *Russ. J. Org. Chem*., 2009, vol. 45, p. 215.
2. Topuzyan, V.O. and Kazandzhyan, M.M., Abstracts of Papers, *XXII Mezhdunarodnaya nauchno-tekhnicheskaya konferentsiya "Khimicheskie reaktivy, reagenty i protsessy malotonazhnoi khimii"* (XXIInd Int. Scientific–Technical Conf. "Chemical Reagents and Processes of Small-Scale Chemistry"). Minsk, 2010, p. 25.
3. Sheldrick, G.M., *SHELXS97, SHELXL97*; Göttingen, Germany: Univ. of Göttingen, 1997.
4. Topuzyan, V.O. and Khachvankyaan, G.Yu., *Khim. Zh. Arm*., 1996, vol. 49, p. 138.