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Derivatives of α,β-Dehydroamino Acids: V. Intramolecular Cyclization of 2-{2-[(*Z*)-1-Benzamido-2-phenylvinyl]acetamidomethyl}benzimidazole

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Abstract—Reaction of 4-benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one with 2-(1*H*-benzimidazol-2-yl)ethaneamine led to the formation of 2-{2-[(*Z*)-1-benzamido-2-phenylvinyl]acetamidomethyl}benzimidazole that in a reaction with hexamethyldisilazane in DMF gave 5-benzylidene-1-(1*H*-benzimidazol-2-yl)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one. In the presence of K_2CO_3 in dioxane the reaction with hexamethyldisilazane resulted in the product of intramolecular addition, *N*-(4-benzyl-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]-benzimidazol-4-yl)benzamide

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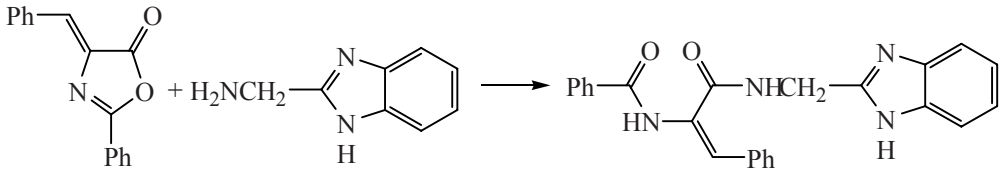
Derivatives of α,β-dehidroamino acids are widely used in organic synthesis. As polyfunctional compounds they are involved into versatile reactions yielding various heterocyclic systems [1]. α,β-Dehydroamino acids derivatives are employed also in the synthesis of nonprotein [2, 3] α-amino acids and physiologically active compounds [4, 5].

This report deals with the study of the intramolecular cyclization of 2-{2-[(*Z*)-1-benzamido-2-phenylvinyl]-acetamidomethyl}benzimidazole (**I**) under various conditions. Amide **I** was obtained from 4-benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one (**II**) and 2-(1*H*-benzimidazol-2-yl)ethaneamine (**III**) in chloroform at room temperature (Scheme 1).

We recently demonstrated that primary amides [6] and hydrazides [7] of N-substituted α,β-dehydroamino acids in the reaction with 1,1,1,3,3,3- hexamethyldisilazane (HMDS) suffered dehydration giving the corresponding 5-imidazolones. In order to synthesize 5-benzylidene-1-(1*H*-benzimidazol-2-yl)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (**IV**) amide **I** was treated with HMDS in DMF at boiling for 2 h. Therewith compound **IV** was obtained in 42% yield (Scheme 2).

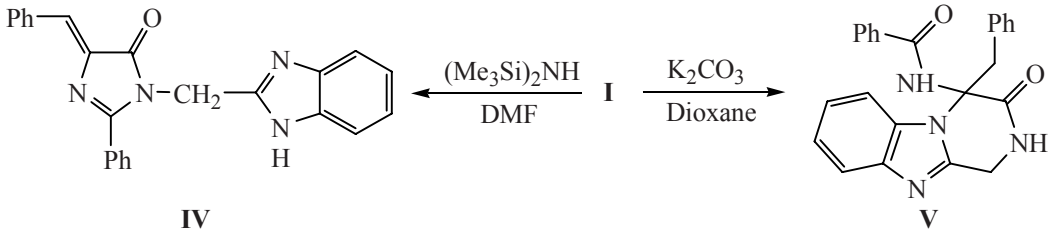
It is known that with respect to nitrogen heterocycles the α,β-dehydroamino acids derivatives can serve as substrates in Michael addition [8–12]. The presence in the molecule of amide **I** both of fragments of α,β-dehydroamino acid and benzimidazole suggests that under certain conditions the compound can undergo an intramolecular cyclization. To investigate this possibility we boiled amide **I** in dioxane in the presence of potassium carbonate for 15 h. The reaction progress was monitored by TLC. After 12 h three spots were found with R_f 0.44, 0.54, and 0.60. The spot corresponding to the initial amide **I**

Scheme 1.



II **III** **I**

Scheme 2.



IV **V**

(R_f 0.54) totally disappeared after 15 h. Then from the reaction mixture tricyclic benzamide **V** was isolated in 63% yield and substituted imidazolone **IV**, in 21% yield (Scheme 2). Tricycle **V** is a previously unknown modification of imidazo[1,2-*a*]pyrazine [13, 14].

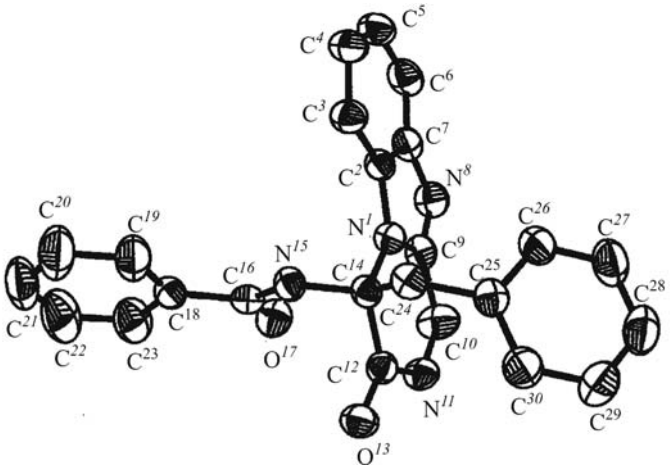


Fig. 1. Structure of *N*-(4-benzyl-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-4-yl)benzamide (**V**); numeration of atoms adopted in this report. Ellipsoids of thermal oscillations are shown on the level of 50% probability.

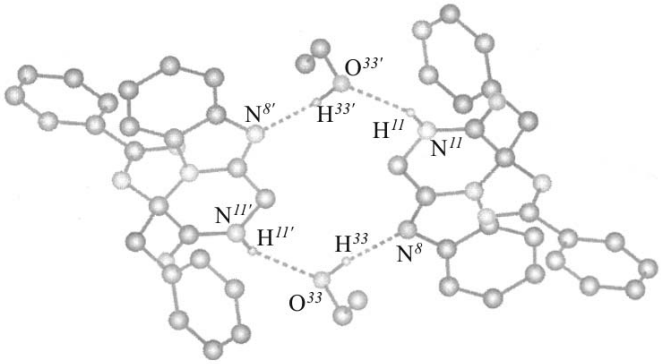


Fig. 2. Dimer of *N*-(4-benzyl-3-oxo-1,2,3,4-tetrahydropyrazino[1,2-*a*]benzimidazol-4-yl)benzamide (**V**) consisting of D- and L-forms of the molecule connected with solvent (ethanol) molecules by double hydrogen bonds

The structure of compound **V** was established by XRD analysis. Its molecules crystallized with solvent molecules (ethanol) in 1:1 ratio (Fig. 1). The compound is racemic. In the crystal the D- and L-forms of the molecule of the studied compound are bound into dimers by double hydrogen bonds $N^{8}\cdots H^{33}–O^{33}\cdots H^{11'}–N^{11'}$ [2.815(3) Å] and $N^{8}\cdots H^{33'}–O^{33'}\cdots H^{11}–N^{11}$ [2.904(3) Å] (Fig. 2), and the dimers are connected into a three-dimensional network by hydrogen bonds $N^{15}–H^{15}\cdots O^{13''}$ [2.965(2) Å].

EXPERIMENTAL

IR spectra of compounds were recorded on a spectrophotometer Specord M-80. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury 300. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent toluene–hexane–ethanol, 1:1.5:1, development under UV radiation and in iodine vapor.

XRD analysis. XRD study was performed on a transparent colorless crystal of the size 0.4 × 0.35 × 0.3 mm. The measurement of 9766 independent reflections was carried out on an automatic diffractometer CAD-4 Enraf Nonius. Crystals of compound **V** monoclinic, space group C2/c, *a* 30.073(6), *b* 8.660(2), *C* 20.854(4) E, β 124.10(3) deg. The structure was solved by the direct method using the program SHELXTL [15]. The hydrogen atoms coordinate were defined from the difference Fourier synthesis of the electronic density. Finally all atomic coordinates including the hydrogen atoms and anisotropic thermal parameters of the nonhydrogen atoms were refined together in the full-matrix least-squares method, the final R-factor equaled 0.051.

2-{2-[(*Z*)-1-Benzamido-2-phenylvinyl]acetamidomethyl}benzimidazole (I). A mixture of 1.0 g (4 mmol) of 4-benzylidene-2-phenyl-1,3-oxazol-5(4*H*)-one (**II**) [16], 0.88 g(4 mmol) of 2-(1*H*-benzimidazol-2-yl)-ethaneamine, and 0.8 g (1.12 ml, 8 mmol) of triethylamine

in 25 ml of chloroform was left standing at room temperature for 24 h. Chloroform was evaporated on a rotary evaporator, the residue was ground with 30 ml of 50% ethanol, the formed solid mass was filtered off and dried in air. Yield 1.57 g (99%), mp 140–142°C (90% ethanol), R_f 0.54. IR spectrum, ν, cm^{-1}: 3400, 3190, 1675, 1650. ^{1}H NMR spectrum, δ, ppm: 4.64 d (2H, CH_2), 7.10 d (2H$_{arom}$), 7.20–7.40 m (4H$_{arom}$), 7.22 s (1H, CH=C), 7.42–7.60 m (6H$_{arom}$), 8.12 d (2H$_{arom}$), 8.80 t (1H, NH) 10.08 s (1H, NH), 11.40 br.s (1H, NH). Found, %: C 72.50; H 5.24; N 14.36. $C_{24}H_{20}N_4O_2$. Calculated, %: C 72.71; H 5.08; N 14.13.

5-Benzylidene-1-(1*H*-benzimidazol-2-yl-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one (IV). A mixture of 0.5 g (1.26 mmol) of reagent **I** and 0.61 g (0.79 ml, 3.8 mmol) of HMDS in 5 ml of DMF was boiled for 2 h. To the cooled mixture 50 ml of water was added, the solution was acidified with hydrochloric acid to pH 4, the separated precipitate was filtered off. Yield 0.2 g (43%), mp 238–240°C (EtOH), R_f 0.60. IR spectrum, ν, cm^{-1}: 3400, 1710, 1640. ^{1}H NMR spectrum, δ, ppm: 5.08 s (2H, CH_2), 7.02–7.20 m (3H$_{arom}$), 7.18 s (1H, CH=C), 7.34–7.42 m (6H$_{arom}$), 8.04 d (3H$_{arom}$), 8.26 d (2H$_{arom}$), 12.24 br.s (1H, NH). Found, %: C 76.52; H 4.51; N 14.93. $C_{24}H_{18}N_4O$. Calculated, %: C 76.17; H 4.79; N 14.80.

***N*-(4-Benzyl-3-oxo-1,2,3,4-tetrahydropyrazino-[1,2-*a*]benzimidazol-4-yl)benzamide (V).** A mixture of 1.0 g(2.52 mmol) of reagent **I** and 1.74 g (12.6 mmol) of potassium carbonate in 25 ml of dioxane was boiled for 15 h, cooled, 80 ml of water was added, the solution was acidified with hydrochloric acid to pH 4, the separated precipitate was filtered off. Yield 0.63 g (63%), mp 283–285°C (EtOH), R_f 0.44. IR spectrum, ν, cm^{-1}: 3295, 1690, 1650. ^{1}H NMR spectrum, δ, ppm: 3.48 d.d (1H, NCH_2, *J* 17.4, 1.6 Hz), 3.57 d (1H, CH_2Ph, *J* 13.2 Hz), 3.92 d (1H, CH_2Ph, *J* 13.2 Hz), 4.42 d.d (1H, NCH_2, *J* 17.4, 2.7 Hz), 6.53 m (2H$_{arom}$), 7.06 m (2H$_{arom}$), 7.14–7.23 m (3H$_{arom}$), 7.40–7.58 m (4H$_{arom}$), 7.90–8.01 m (3H$_{arom}$), 8.19 d.d (1H, NHC, *J* 2.7, 1.6 Hz), 9.73 s (1H, NH). Found, %: C 72.45; H 5.30; N 14.43. $C_{24}H_{20}N_4O_2$. Calculated, %: C 72.71; H 5.08; N 14.13.

To the ethanol solution water was added, the separated precipitate was filtered off. After recrystallization from 50% ethanol we obtained 0.2 g (21%) of compound **IV**.

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