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LETTERS TO THE EDITOR

UNEXPECTEDLY FACILE HETEROCYCLIZATION OF O-BENZOYL-β-PIPERIDINO-PROPIOAMIDOXIME IN DIMETHYL SULFOXIDE

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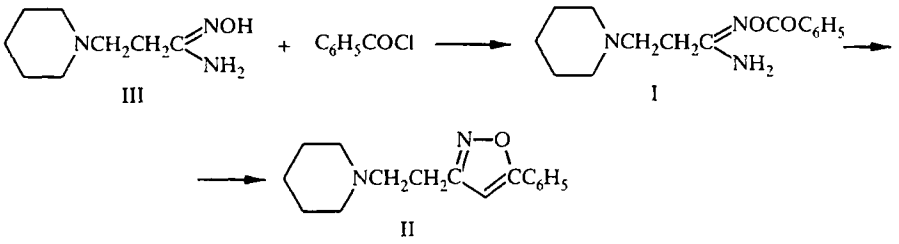
The well-known method for heterocyclization of O-acylamidoximes [1] suggests heating above their melting points; in this case, it is assumed that heating does not change the *syn*-configuration of the amidoximes, which is the only one possible in cyclization.

We have searched for conditions for heterocyclization of the O-benzoylamidoxime of β-piperidinopropionic acid I to 3-(β-piperidino)ethyl-5-phenyl-1,2,4-oxadiazole II in different solvents. We observed that in an attempt at heterocyclization of the hydrochloride I·HCl by heating in benzene and toluene with azeotropic distilling off the water, the starting compound remained unchanged. Carrying out the reaction of benzoylation of amidoxime of β-piperidinopropionic acid III in dimethylformamide at room temperature and at heating up to 100°C the uncyclized hydrochloride I·HCl was obtained in 20% yield.

Smooth heterocyclization of the base O-benzoylamidoxime I to 1,2,4-oxadiazole II was observed when the former was allowed to stand for many hours in dimethyl sulfoxide at room temperature. And as shown by the PMR spectrum of compound I in DMSO-d_6, removal of water begins to occur immediately after the O-benzoylamidoxime I dissolves. A set of signals appears in the spectrum which are due to oxadiazole II; complete I → II conversion occurs in 10 days.



III I II

Prolonged holding of the hydrochloride I·HCl in DMSO did not lead to formation of the hydrochloride II·HCl. The latter was obtained by treatment of II with an alcoholic solution of HCl.

The PMR spectra were recorded on a Mercury-300 instrument (300 MHz), internal standard HMDS. The IR spectra were obtained on UR-20 in KBr pellets. The synthesis of the compounds is described in [2]. For comparison with compounds II and II·HCl, below we give mp 119-120°C (compound I) and mp 78°C (compound I·HCl), and also the spectra of hydrochloride I·HCl. IR spectrum ($CDCl_3$); 1736 ($\nu_{C(C=O)O}$); 1640 ($\nu_{C=N}$ and δ_{N-H});

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2936, 3120, and 3264 cm^{-1} (ν_{NH_2}). PMR spectrum ($CDCl_3$): 7.40-8.04 (5H, m, COC_6H_5); 2.31 (2H, s, NH_2); 1.46 and 1.57 (6H, m, $-NCH_2(\underline{CH_2})_3CH_2-$]; 2.44 m [6H, m, $-N\underline{CH_2}(CH_2)_3\underline{CH_2}-$ and $NCH_2\underline{CH_2}$] and 2.60 ppm (2H, t, J = 7.0 Hz, $NCH_2\underline{CH_2}$). PMR spectrum (DMSO-d_6): 7.17-8.14 (5H, m, COC_6H_5); 6.68 (2H, s, NH_2); 2.62 (2H, t, J = 7.0 Hz, $N\underline{CH_2}CH_2$); 2.44[4H, m, $-N\underline{CH_2}(CH_2)_3\underline{CH_2}$]; 2.34 (2H, t, J = 7.0 Hz, $NCH_2\underline{CH_2}$); 1.36 and 1.50 ppm (6H, m, $-NCH_2(\underline{CH_2})_3CH_2-$].

3-(β-Piperidino)ethyl-5-phenyl-1,2,4-oxadiazole (II). Solution of amidoxime I (0.5 g, 1.8 mmol) in 10 ml of DMSO was held at ~20°C for 10 days. Then the solvent was distilled off in vacuum; the residue was dissolved in chloroform and precipitated by hexane. Obtained: 0.34 g (73%); mp 83°C. Found, %: C 70.09; H 7.52; N 16.25. $C_{15}H_{19}N_3O$. Calculated, %: C 70.01; H 7.44; N 16.33. IR spectrum: 1648 ($\nu_{C=N}$), 1584 ($\nu_{C=C}$), 2944, 3104, and 3256 cm^{-1} (ν_{NH_2}). PMR spectrum (DMSO-d_6): 7.25-7.86 (5H, m, COC_6H_5); 3.83 (2H, t, J = 7.0 Hz, $N\underline{CH_2}CH_2$); 3.30 and 3.46 [4H, t, J = 7.0 Hz, $-N\underline{CH_2}(CH_2)_3\underline{CH_2}-$]; 3.15 (2H, t, J = 7.0 Hz, $NCH_2\underline{CH_2}$); 1.52, 1.72, and 1.83 ppm [6H, m, $-NCH_2(CH_2)_3\underline{CH_2}-$].

3-(β-Piperidino)ethyl-5-phenyl-1,2,4-oxadiazole Hydrochloride (II·HCl). An alcoholic solution of HCl was added to solution of oxadiazole II (0.39 g) in chloroform until pH 5 was reached. After addition of hexane, 0.34 g (95%) of hydrochloride II·HCl was obtained; mp 125-126°C. Found, %: C 61.38; H 6.93; Cl 12.15; N 14.40. $C_{15}H_{20}ClN_3O$. Calculated, %: C 61.32; H 6.86; Cl 12.07; N 14.30. IR spectrum: 1664 ($\nu_{C=N}$ and ν_{N-H}); 2300-3100 cm^{-1} (ν_{C-H} and ν_{N-H}). PMR spectrum (DMSO-d_6): 13.03 (1H, s, NH); 7.48-7.97 (5H, m, COC_6H_5); 3.84 (2H, t, J = 7.0 Hz, $N\underline{CH_2}CH_2$); 3.36 and 3.46 [4H, t, J = 7.0 Hz, $-N\underline{CH_2}(CH_2)_3\underline{CH_2}-$]; 3.12 (2H, t, J = 7.0 Hz, $NCH_2\underline{CH_2}$); 1.50, 1.76, and 1.86 ppm [6H, m, $-NCH_2(\underline{CH_2})_3CH_2-$].

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REFERENCES

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