Cyclization of *O*-benzoyl-β-piperidinopropionamidoximes to form 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles

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The reactions of β-piperidinopropionamidoxime with substituted benzoyl chlorides afforded *O*-benzoylation products, which underwent cyclization to form 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles upon heating in dimethylformamide in the presence of molecular sieves at 60 °C for 1—2.5 h. Heating of *O*-benzoyl-β-piperidinopropionamidoxime in dimethylformamide in the presence of K_2CO_3 at 85 °C for 4 h afforded a mixture of 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole, benzoic acid, and *N*-(β-piperidino)ethylurea.

Key words: *O*-benzoyl-β-piperidinopropionamidoximes, dimethylformamide, 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles, Beckmann rearrangement, *N*-(β-piperidino)ethylurea.

Amino acids and their derivatives play an important role in all life processes. The synthesis, isolation, physicochemical characteristics, and biological properties of amino acids and their derivatives are topical fields of research. Thus, hydrolysis of natural antibiotics tuberactinomycins A and N afforded derivatives of amino acids, *viz.*, *threo*-γ-hydroxy-β-lysine and the *erythro* isomer of a β-alanine derivative.[1] In the present study, we examined derivatives of primary amidoximes of β-aminopropionic acids and used the piperidine group as the β-amino fragment. It is known that many compounds containing piperidine fragments are pharmaceuticals exhibiting various therapeutic effects.[2] Due to the presence of the primary amidoxime group, these compounds can be widely used as synthons possessing the ambident reactivity.

In the present study, we carried out acylation of β-piperidinopropionamidoxime with substituted benzoyl chlorides and subjected the resulting *O*-acyl derivatives to dehydration with the aim of preparing 1,2,4-oxadiazoles. Previously, it has been demonstrated that some amidoximes, their *O*-acyl derivatives, and products of dehydration of the latter, *viz.*, 1,2,4-oxadiazoles, exhibit psychotropic properties.[3] β-Aminopropionamidoximes show cytostatic activity.[4] We revealed local anesthetic, antiarythmic, and tuberculostatic properties of *O*-acyl-β-aminopropionamidoximes.[5]

Results and Discussion

The synthesis of *O*-acylated amidoximes attracts the attention of researchers primarily as an approach to 1,2,4-oxadiazoles.[6—8] Previously, cyclodehydration of *O*-acylamidoximes giving rise to 1,2,4-oxadiazoles has been carried out in solutions of acetic acid or acetic anhydride in water, dilute sodium hydroxide, sulfuric acid,[9] diphenyl ether,[7] or toluene.[10] Spontaneous cyclodehydration of amidoxime *O*-ethers (without their isolation) proceeds in pyridine.[11]

We prepared β-piperidinopropionamidoxime (**2**) starting from β-piperidinopropionitrile (**1**). Compound **2** was used for the synthesis of *O*-aroyl-β-piperidinopropionamidoximes (**3a—f**) by either acylation with substituted benzoyl chlorides in benzene in the presence of triethylamine (compounds **3a—c**) or upon treatment of hydrochlorides of acylation products with K_2CO_3 (compounds **3d—f**) (Scheme 1). The results of elemental analysis, physicochemical characteristics, and spectroscopic data for compounds **3a—f** are given in Tables 1—4.

X-ray diffraction analysis of *O*-aroyl-β-piperidinopropionamidoxime hydrochlorides (**3a** · HCl and **3c** · HCl)[12] confirmed that the reaction proceeded at the O atom of the amidoxime group. It was also found that the C—NH_2 and O—C(O) bonds are in the *syn* orientation with respect to the C=N bond and that the C=N.

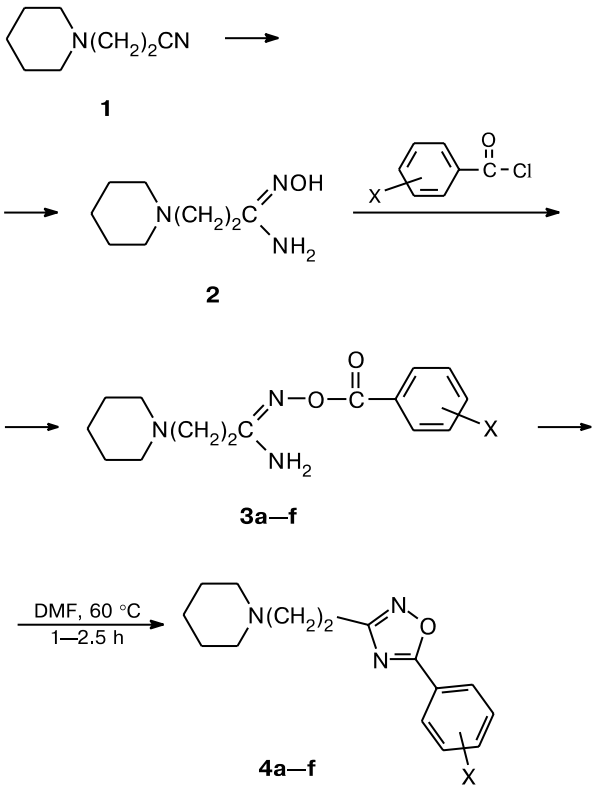
The IR spectra of compounds **3a—f** have characteristic stretching absorption bands of the C(=O)O ester group (1728—1736 cm^{-1}) and the amino group (3110—3500 cm^{-1}) as well as intense bands of the C=C double bond at 1564—1638 cm^{-1} (see Table 2).

The ^1H NMR spectra of *O*-aroyl-β-piperidinopropionamidoximes **3a—f** show signals for the aroyl groups (δ 7.00—8.29). The spectra of compounds **3a,b** have signals of the *p*-Me and *p*-MeO groups at δ 2.37 and 2.50, respectively. The signals for the protons of the NH_2 groups are observed at δ 6.57—6.77, and the signals for the pro-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1945—1950, November, 2002.

1066-5285/02/5111-2100 $27.00

Scheme 1



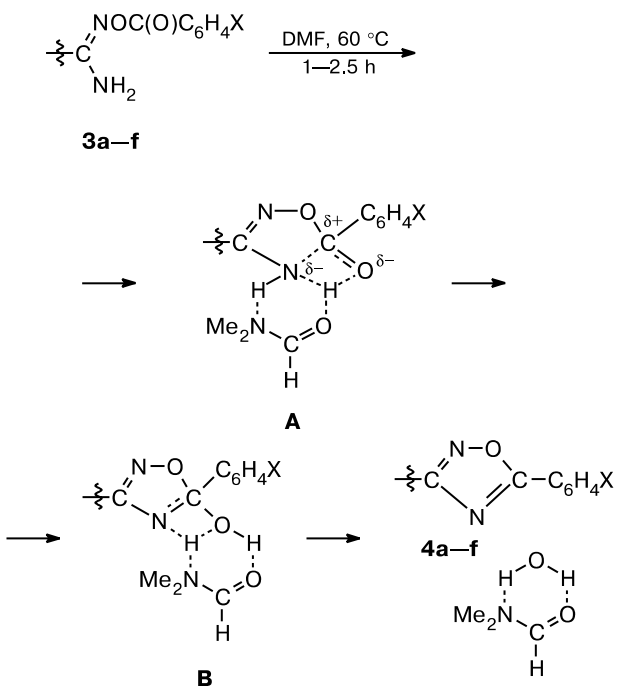
X = *p*-Me (**a**), *p*-MeO (**b**), H (**c**), *p*-Br (**d**), *m*-Cl (**e**), *p*-NO_2 (**f**)

tons of three methylene groups of the piperidine ring are observed as two multiplets at δ ~1.40 and 1.55. The protons of the α- and β-methylene groups give triplets at δ 2.27—2.38 and 2.36—3.10, respectively. The methylene groups of the piperidine ring bound to the N atom give a multiplet with the intensity of four protons (δ 2.37—2.56) (see Table 3).

The ^{13}C NMR spectra of compounds **3a—f** show signals for the carbonyl carbon atom of the ester group at δ 161.9—170.0 and a signal for the C atom of the amidoxime group ($\underline{C}(=NOCOC_6H_4X)NH_2$) at δ 157.3—169.2. Six signals for the aromatic C atoms of the substituted benzene ring are observed at δ 125.1—144.4 (see Table 4).

Previously,[13] when recording the ^1H NMR spectrum of compound **3c** in DMSO-d_6 at ~20 °C, we have found that the base of *O*-benzoyl-β-piperidinopropionamidoxime (**3c**) was readily transformed into 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (**4c**). In the present study, we performed dehydration leading to heterocyclization of *O*-aroylamidoximes **3a—f** with the formation of oxadiazoles **4a—f** by heating in DMF in the presence of molecular sieves (4 Å) for 1—2.5 h (see Scheme 1). Although DMSO and DMF have close dielectric permeabilities, the latter solvent has the lower boiling point, which is more convenient for the preparative use. The function of bipolar aprotic DMF in the dehydration reaction of *O*-aroyl-β-aminopropionamidoximes **3a—f** is to stabilize the transition states **A** and **B** *via* intermolecular hydrogen bonding (Scheme 2).

Scheme 2



It was found that heterocyclization of compounds **3d—f** containing electron-withdrawing substituents proceeded faster (TLC control) and was completed in 1 h, whereas heterocyclization of compounds **3a,b** bearing electron-releasing substituents as well as of *O*-benzoyl-β-piperidinopropionamidoxime (**3c**) was completed in 2.5 h. Apparently, the activation barriers of the formation of the transition state **A** stabilized by the $N^{\delta-}...C^{\delta+}$ interaction are lower for compounds **3d—f** containing the electron-withdrawing substituents in the C_6H_4X fragment, which increase the fractional positive charge on the carbonyl C atom.

In the IR spectra of compounds **4a—f**, stretching bands of the C(=O)O ester groups and the amino group are absent. These spectra show intense stretching absorption bands of the C=C double bonds (1584—1600 cm^{-1}) and powerful stretching absorption bands of the C=N bonds (1652—1660 cm^{-1}) (see Table 2).

The ^1H NMR spectroscopic data for compounds **4a—f** are given in Table 3. The spectra of these compounds differ radically from those of compounds **3a—f** in that they have no signals of the NH_2 group, whereas the signals for the protons of three methylene groups $C—(CH_2)_3—C$ of the piperidine ring are observed as multiplets with the

Table 1. Yields, retention factors, melting points, and data from elemental analysis of *O*-aroyl-β-piperidinopropionamidoximes **3a—f**, 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4a—f**, and *N*-(β-piperidino)ethylurea hydrochloride (**5**·HCl)

Compound	Yield (%)	R_f	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
				C	H	Hal	N	
3a	93	0.76	78 (Pr^iOH)	65.80 / 65.43	7.63 / 7.68	—	14.89 / 15.26	$C_{16}H_{23}N_3O_2$
3b	83	0.76	96 (EtOH)	62.87 / 62.93	7.54 / 7.59	—	13.62 / 13.76	$C_{16}H_{23}N_3O_3$
3c	93	0.74	61 (EtOH)	65.52 / 65.43	7.49 / 7.68	—	15.11 / 15.26	$C_{15}H_{21}N_3O_2$
3d	84	0.75	92 (Pr^iOH)	50.64 / 50.86	5.72 / 5.69	22.43 / 22.56	11.75 / 11.86	$C_{15}H_{20}BrN_3O_2$
3e	86	0.66	74 (EtOH)	58.23 / 58.16	6.47 / 6.51	11.39 / 11.44	13.68 / 13.56	$C_{15}H_{20}ClN_3O_2$
3f	89	0.69	87 (Pr^iOH)	56.35 / 56.24	6.24 / 6.29	—	17.33 / 17.49	$C_{15}H_{20}N_4O_4$
4a	67	0.84	108 (Pr^iOH)	70.76 / 70.82	7.84 / 7.80	—	15.62 / 15.48	$C_{16}H_{21}N_3O$
4b	70	0.82	102 (EtOH)	66.92 / 66.87	7.44 / 7.37	—	14.84 / 14.62	$C_{16}H_{21}N_3O_2$
4c	72	0.76	83 (EtOH)	70.09 / 70.01	7.52 / 7.44	—	16.25 / 16.33	$C_{15}H_{19}N_3O$
4d	73	0.89	114 (Pr^iOH)	53.72 / 53.58	5.44 / 5.39	23.84 / 23.76	12.56 / 12.50	$C_{15}H_{18}BrN_3O$
4e	70	0.75	96 (Pr^iOH)	61.81 / 61.75	6.27 / 6.21	14.53 / 12.15	14.61 / 14.40	$C_{15}H_{18}ClN_3O$
4f	68	0.79	109 (EtOH)	60.07 / 59.59	6.28 / 6.00	—	18.83 / 18.53	$C_{15}H_{18}N_4O_3$
5·HCl	23	—	208 (EtOH)	43.51 / 43.33	8.35 / 8.18	16.35 / 15.99	25.07 / 25.27	$C_8H_{18}ClN_3O$

Table 2. IR spectra of *O*-aroyl-β-piperidinopropionamidoximes **3a—f** and 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4a—f**

Compound	X	ν(C(=O)O)	ν(C=N), δ(N—H)	ν(C=C)	ν(C—N)	ν(N—O), ν(C—O)	ν(NH_2)
		cm^{-1}					
3a	*p*-Me	1732	1684	1636	1268	1120, 1092	3120, 3376, 3496
3b	*p*-MeO	1732	1636	1588	1268	1112, 1096	3200, 3328, 3472
3c	H	1736	1632	1608	1272	1072, 1096	2936, 3120, 3264
3d	*p*-Br	1732	1632	1598	1268	1104, 1064	3104, 3376, 3496
3e	*m*-Cl	1736	1632	1576	1248	1120, 1068	3200, 3376, 3496
3f	*p*-NO_2	1728	1632	1564	1276	1124, 1096	3112, 3304, 3480
4a	*p*-Me	—	1652	1596	1264	1016, 1072	—
4b	*p*-MeO	—	1656	1590	1276	1112, 1072	—
4c	H	—	1652	1584	1272	1116, 1068	—
4d	*p*-Br	—	1656	1588	1276	1068, 1120	—
4e	*m*-Cl	—	1656	1594	1276	1080, 1120	—
4f	*p*-NO_2	—	1660	1600	1274	1068, 1120	—

average values at δ 1.50, 1.70, and 1.80. The signals of the α- and β-methylene groups of 1,2,4-oxadiazoles **4a—f** are shifted downfield as compared to those of *O*-aroyl derivatives **3a—f** (δ 3.05—3.12 and 3.77—3.80, respectively). The methylene groups bound to the N atom of the piperidine ring each give two signals with the intensities of two protons for the axial and equatorial protons. The half-width of the signals for H_{eq} (δ ~3.30) is smaller (22 Hz)

Table 3. ^{1}H NMR spectra of *O*-aroyl-β-piperidinopropionamidoximes **3a—f** and 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4a—f** (in DMSO-d_6)

Compound	X	δ (*J*/Hz)					
		$(CH_2)_3$ (m)	$N(CH_2)_2$ (m)	α-CH_2 (t)	β-CH_2 (t)	NH_2	COC_6H_4X
3a	*p*-Me	1.39, 1.52	2.54 (4 H)	2.30 (*J* = 7.2)	2.36 (*J* = 7.2)	6.62	2.37 (*p*-Me); 7.30, 8.04 (both d, 2 H each, *J* = 8.7)
3b	*p*-MeO	1.40, 1.51	2.50 (4 H)	2.33 (*J* = 7.0)	2.60 (*J* = 7.0)	6.61	2.50 (*p*-MeO); 7.00, 8.05 (both d, 2 H each, *J* = 8.3)
3c	H	1.37, 1.50	2.37 (4 H)	2.26 (*J* = 7.0)	2.54 (*J* = 7.0)	6.58	7.40—8.10 (m, 5 H)
3d	*p*-Br	1.37, 1.49	2.37 (4 H)	2.27 (*J* = 7.0)	2.54 (*J* = 7.0)	6.57	7.50, 8.09 (both d, 2 H each, *J* = 8.3)
3e	*m*-Cl	1.41, 1.56	2.56 (4 H)	2.38 (*J* = 7.0)	2.72 (*J* = 7.0)	6.77	7.54—8.06 (m, 4 H)
3f	*p*-NO_2	1.40, 1.60	2.53 (4 H)	2.27 (*J* = 7.2)	3.10 (*J* = 7.2)	6.60	8.22, 8.29 (both d, 2 H each, *J* = 8.4)
4a	*p*-Me	1.53, 1.70, 1.86	3.33 (2 H_{eq}); 3.50 (2 H_{ax})	3.12 (*J* = 7.0)	3.80 (*J* = 7.0)	—	2.16 (*p*-Me); 7.01, 7.69 (both d, 2 H each, *J* = 8.0)
4b	*p*-MeO	1.54, 1.75, 1.84	3.33 (2 H_{eq}); 3.44 (2 H_{ax})	3.12 (*J* = 7.0)	3.80 (*J* = 7.0)	—	2.26 (*p*-MeO); 7.75, 8.76 (both d, 2 H each, *J* = 8.7)
4c	H	1.52, 1.72, 1.83	3.33 (2 H_{eq}); 3.46 (2 H_{ax})	3.15 (*J* = 7.0)	3.83 (*J* = 7.0)	—	7.25—7.86 (m, 5 H)
4d	*p*-Br	1.50, 1.70, 1.85	3.30 (2 H_{eq}); 3.40 (2 H_{ax})	3.07 (*J* = 7.8)	3.77 (*J* = 7.8)	—	7.43, 7.74 (both d, 2 H each, *J* = 8.1)
4e	*m*-Cl	1.50, 1.70, 1.82	3.28 (2 H_{eq}); 3.41 (2 H_{ax})	3.07 (*J* = 8.1)	3.77 (*J* = 8.1)	—	7.23—7.77 (m, 4 H)
4f	*p*-NO_2	1.50, 1.71, 1.81	3.29 (2 H_{eq}); 3.40 (2 H_{ax})	3.05 (*J* = 7.5)	3.77 (*J* = 7.5)	—	8.07, 8.20 (both d, 2 H each, *J* = 9.0)

Table 4. ^{13}C NMR spectra of *O*-aroyl-β-piperidinopropionamidoximes **3a—f** and 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4a—f**

Compound	X	δ							
		C=O (**3**) or C(5)=N (**4**)	C=N (**3**) or C(3)=N (**4**)	α-CH_2	β-CH_2	$N(CH_2)_2$	$(CH_2)_3$	C arom.	C_X
3a	*p*-Me	166.8	166.3	29.0	58.3	61.8	18.5, 19.4	125.1, 126.5, 127.0, 138.7	19.5 (*p*-Me)
3b	*p*-MeO	164.4	157.3	26.4	53.7	53.0	22.2, 23.4	127.4, 130.2, 130.5, 144.4	22.3 (*p*-MeO)
3c	H	163.0	158.2	27.5	55.6	53.2	23.6, 25.2	128.1, 128.9, 129.2, 132.4	—
3d	*p*-Br	163.0	158.2	27.5	53.2	55.6	23.6, 27.5	128.1, 128.9, 129.3, 132.4	—
3e	*m*-Cl	161.9	157.9	26.9	54.8	52.8	23.0, 24.4	127.3, 127.7, 128.5, 131.1	—
3f	*p*-NO_2	170.0	169.2	32.9	62.1	65.6	22.4, 23.3	130.4, 131.1, 132.7, 134.8	—
4a	*p*-Me	168.1	167.8	30.5	59.8	63.4	20.1, 20.4	127.1, 128.6, 136.7, 138.4	20.9 (*p*-Me)
4b	*p*-MeO	168.1	159.6	30.6	59.8	63.3	20.1, 21.0	127.2, 127.5, 128.7, 129.0	24.9 (*p*-MeO)
4c	H	168.0	167.8	30.5	59.8	63.3	20.1, 21.0	126.4, 127.6, 128.5, 141.2	—
4d	*p*-Br	168.7	158.5	26.5	54.6	52.2	22.7, 26.5	127.8, 130.5, 131.2, 133.4	—
4e	*m*-Cl	163.0	156.3	26.9	63.1	55.2	22.3, 24.2	127.4, 130.0, 133.5, 137.2	—
4f	*p*-NO_2	170.0	169.2	25.5	57.8	53.2	22.1, 22.7	128.5, 134.8, 138.0, 151.8	—

Note. The ^{13}C NMR spectra of compounds **3a—f**, **4a,b**, and **4c—f** were recorded in DMSO, $CHCl_3$, and a 1 : 1 $CHCl_3$—MeOH mixture, respectively.

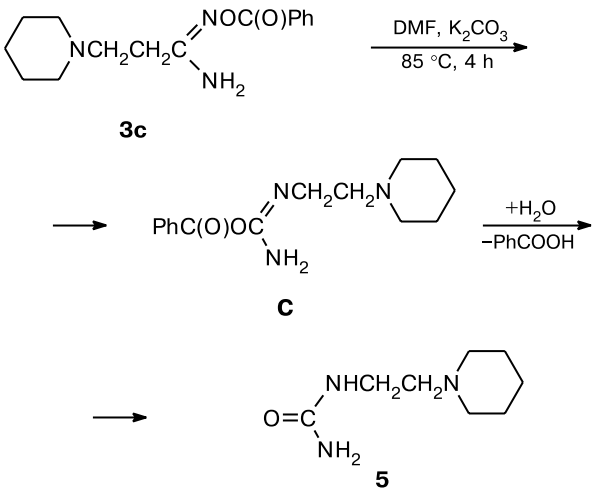
than that of the signals for H_{ax} (δ ~3.45, 27 Hz). The signals for the aromatic protons of 1,2,4-oxadiazoles **4a—f** are observed at δ 7.01—8.76.

Based on the ^{1}H NMR spectra, it can be concluded that the transformation of *O*-aroyl-β-piperidinopropionamidoximes **3a—f** to 5-aroyl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4a—f** under the conditions in which the NMR spectra were recorded leads to deceleration of the piperidine-ring inversion because the system becomes more rigid.

In the ^{13}C NMR spectra of compounds **4a—f**, the signals for the C(3) and C(5) atoms of the 1,2,4-oxadiazole ring are observed at δ 156.3—169.2 and 163.0—170.0, respectively. The assignments of the signals for the C atoms of the C(3)=N and C(5)=N bonds were made based on the comparison of the electronegativities of the O and N atoms in the 1,2,4-oxadiazole ring. Thus, the set of signals observed at lower field was assigned to the C atoms of the C(5)=N bond because the C(5) atom is bound to the more electronegative O atom. The signals for the α- and β-methylene C atoms are observed at δ 25.5—30.6 and 54.6—63.1, respectively. The C atoms of the benzene ring give signals at δ 126.4—151.8 (see Table 4).

Heating of *O*-benzoyl-β-piperidinopropionamidoxime (**3c**) in DMF at 85 °C for 4 h afforded 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (**4c**) (R_f 0.76), *N*-(β-piperidino)ethylurea (**5**) (R_f 0.29), and benzoic acid (R_f 0.80) (Scheme 3). Compound **5** was characterized as hydrochloride **5**·HCl (see Table 1). The formation of urea **5** occurred through the Beckmann rearrangement, which was described for *O*-acylamidoximes.[14] However, elimination of the acyl-containing residue has not previously been observed.

Scheme 3



Benzoic acid and urea **5** can be generated by the reaction of the intermediate rearrangement product **C** with the water molecule liberated upon dehydration of **3c** to form 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (**4c**).

Therefore, acylation of β-piperidinopropionamidoxime (**2**) with substituted benzoyl chlorides proceeds at the O atom of the amidoxime group. Dehydration of *O*-aroylamidoximes **3** on heating in DMF (60 °C) in the presence of molecular sieves (4 Å) for 1—2.5 h afforded 5-aryl-3-(β-piperidino)ethyl-1,2,4-oxadiazoles **4**. Heating of *O*-benzoyl-β-piperidinopropionamidoxime (**3c**) in the presence of potassium carbonate at 85 °C for 4 h gave *N*-(β-piperidino)ethylurea (**5**), benzoic acid, and 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (**4c**).

Experimental

The ^1H and ^{13}C NMR spectra were recorded on Mercury-300 (300 MHz) and Bruker (20.13 MHz) instruments, respectively, with HMDS as the internal standard. The IR spectra were measured on a UR-20 instrument in KBr pellets. The course of the reactions was monitored by TLC on Sorbfil plates (benzene—MeOH, 1 : 3, as the eluent).

Nitrile **1** was synthesized according to a procedure described previously.[15] The procedure for the preparation of amidoxime **2** has been developed by us earlier.[16]

The solvents used for acylation ($CHCl_3$ and benzene), dehydration (DMF), precipitation, recrystallization (hexane, EtOH, Pr^iOH, and AcOEt), and TLC (MeOH and benzene) were purified according to standard procedures.[17]

***O*-Benzoyl-β-piperidinopropionamidoxime (3a).** A solution of benzoyl chloride (0.41 g, 2.9 mmol) in dry $CHCl_3$ (5 mL) was added dropwise with stirring to a mixture of β-piperidinopropionamidoxime (**2**) (0.5 g, 2.9 mmol), dry $CHCl_3$ (25 mL), and Et_3N (0.4 mL, 2.9 mmol) at ~20 °C. The reaction mixture was stirred at ~20 °C for 8 h. The solvent was distilled off on a rotary evaporator and then water (5 mL) was added to the residue. The precipitate that formed was filtered off, dried, and recrystallized from Pr^iOH. Compound **3a** was obtained in a yield of 0.74 g (93%).

Compounds **3b,c** were prepared analogously.

***O*-(*p*-Nitrobenzoyl)-β-piperidinopropionamidoxime (3f).** A solution of *p*-nitrobenzoyl chloride (1.09 g, 5.9 mmol) in dry benzene (5 mL) was added with stirring to a mixture of amidoxime **2** (1.02 g, 5.9 mmol) and dry benzene (35 mL) at ~20 °C. After 10 h, *O*-(*p*-nitrobenzoyl)-β-piperidinopropionamidoxime hydrochloride (**3f**·HCl) was filtered off in a yield of 1.76 g (5.2 mmol), which was dissolved in distilled water (5 mL). Then K_2CO_3 (0.36 g, 2.6 mmol) was added. The precipitate that formed was filtered off and recrystallized from EtOH. Compound **3f** was obtained in a yield of 1.40 g (89%).

O-Aroyl-β-piperidinopropionamidoximes **3d,e** were prepared analogously.

The yields, retention factors, physicochemical characteristics, spectroscopic data, and results of elemental analysis of *O*-acylamidoximes **3a—f** are given in Tables 1—4.

5-(*p*-Bromophenyl)-3-(β-piperidino)ethyl-1,2,4-oxadiazole (4d). A solution of *O*-(*p*-bromobenzoyl)-β-piperidinopropionamidoxime (**3d**) (0.52 g, 1.5 mmol) was heated with stirring in DMF in the presence of molecular sieves (4 Å) at 60 °C for 1 h. Then the molecular sieves were filtered off and washed on the filter with benzene. The solvents were evaporated *in vacuo* with the successive use of a water-jet and an oil pump. Hexane was added to the residue. The precipitate that formed was filtered off and recrystallized from EtOH. Oxadiazole **4d** was obtained in a yield of 0.36 g (73%).

1,2,4-Oxadiazoles 4a—c,e,f were prepared analogously. Dehydration of the compounds containing electron-withdrawing substituents in the benzene ring (**3d—f**) was completed in 1 h. Dehydration of the compounds bearing electron-releasing sub-

stituents (**3a,b**) and the compound with the unsubstituted benzene ring (**3c**) was completed in 2.5 h.

The yields, retention factors, physicochemical characteristics, spectroscopic data, and results of elemental analysis of 1,2,4-oxadiazoles **4a—f** are given in Tables 1—4.

5-Phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (4c) and *N*-(β-piperidino)ethylurea (5). A solution of *O*-benzoyl-β-piperidinopropionamidoxime (**3c**) (0.28 g, 1 mmol) in dried DMF (5 mL) was heated with K_2CO_3 (0.1 g, 0.7 mmol) at 85 °C for 4 h (TLC control). The solvent was evaporated *in vacuo* using a water-jet pump and then distilled water (2 mL) was added to the residue. After trituration of the residue, benzoic acid was obtained in a yield of 0.03 g (24%), m.p. 120 °C, R_f 0.80. The aqueous filtrate was extracted with benzene. The benzene layer was separated, dried over calcined K_2CO_3, and evaporated *in vacuo*. The residue was triturated in hexane to obtain 5-phenyl-3-(β-piperidino)ethyl-1,2,4-oxadiazole (**4c**) in a yield of 0.08 g (32%), R_f 0.76. Found (%): C, 70.12; H, 7.64; N, 16.43. $C_{15}H_{19}N_3O$. Calculated (%): C, 70.01; H 7.44; N, 16.33. The aqueous filtrate was concentrated. The organic residue was dried by the addition of benzene (2×5 mL) and vacuum distillation using a water-jet pump. The residue was dissolved in anhydrous EtOH (0.5 mL). Then a solution of HCl in EtOH was added to pH 3. *N*-(β-Piperidino)ethylurea hydrochloride (**5**·HCl) was precipitated with ethyl acetate in a yield of 0.05 g (23%). IR, ν/cm^{-1}: 1604 (δ(N—H)), 1664 (ν(C=O)), 3048 ($\nu_s(NH_2)$), 3264 ($\nu_{as}(NH_2)$). ^{1}H NMR (DMSO-d_6), δ: 1.55, 1.76, and 1.86 (all m, 6 H, $-N(CH_2)_2(C\underline{H}_2)_3$); 3.11 (t, 2 H, $C\underline{H}_2N(CH_2)_2$, J = 7.0 Hz); 3.33 (m, 2 H, NCH_2 (H_{eq})); 3.49 (m, 2 H, NCH_2 (H_{ax})); 3.84 (t, 2 H, $(C\underline{H}_2CH_2N(CH_2)_2$, J = 7.0 Hz); 7.37 (s, 2 H, NH_2). ^{13}C NMR (DMSO), δ: 20.1 (1 C, $N(CH_2)_2(CH_2)_2\underline{C}H_2$); 21.0 (2 C, $-N(CH_2)_2(\underline{C}H_2)_2CH_2$); 30.6 (1 C, $NHCH_2\underline{C}H_2N$); 59.8 (1 C, $NH\underline{C}H_2CH_2N$); 63.4 (2 C, $N(\underline{C}H_2)_2(CH_2)_2CH_2$); 167.6 (1 H, C=O).

This study was in part financially supported by the US Civilian Research and Development Foundation (CRDF, Grant KB2-2314-AL-02).

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Received October 8, 2001;
in revised form March 25, 2002