The Synthesis of β-Heteroarylamino-α,β-dehydro-α-amino Acid and β-Heteroarylamino-α-amino Acid Derivatives

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Dedicated to Professor Hans Junek, University of Graz, on the occasion his 60th birthday.

From heteroarylaminomethyleneoxazolones **4**, obtained from *N*-heteroarylformamidines **2** and 2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**3**), the following β-heteroarylamino-α,β-dehydro-α-amino acid derivatives were prepared: methyl **8** and ethyl esters **9**, amides **10** and **11**, hydrazides **12**, and azides **15**. By catalytic hydrogenation the compounds **4** were converted into β-heteroarylamino substituted amides **18** and β-heteroarylamino-α-amino acids **20**.

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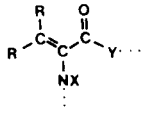
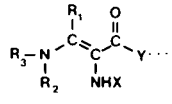
Dehydroamino acids are of major interest in the area of bioactive dehydropeptides and of asymmetric hydrogenation [1-4]. Recently, a review has appeared covering the α,β-dehydroamino acids and α,β-dehydropeptides with the structural unit A [4].

In this paper we report on the synthesis of β-heteroarylamino-α,β-dehydro-α-amino acids and derivatives with the structural unit B (Scheme 1).

Scheme 1



A



B

Y = O, N

X = HCO, MeCO, ArCO, alkylOOC–, α-aminoacyl

R = H, alkyl, aryl, heteroaryl

X = H, ArCO

Y = O, N

R_1 = H, Me

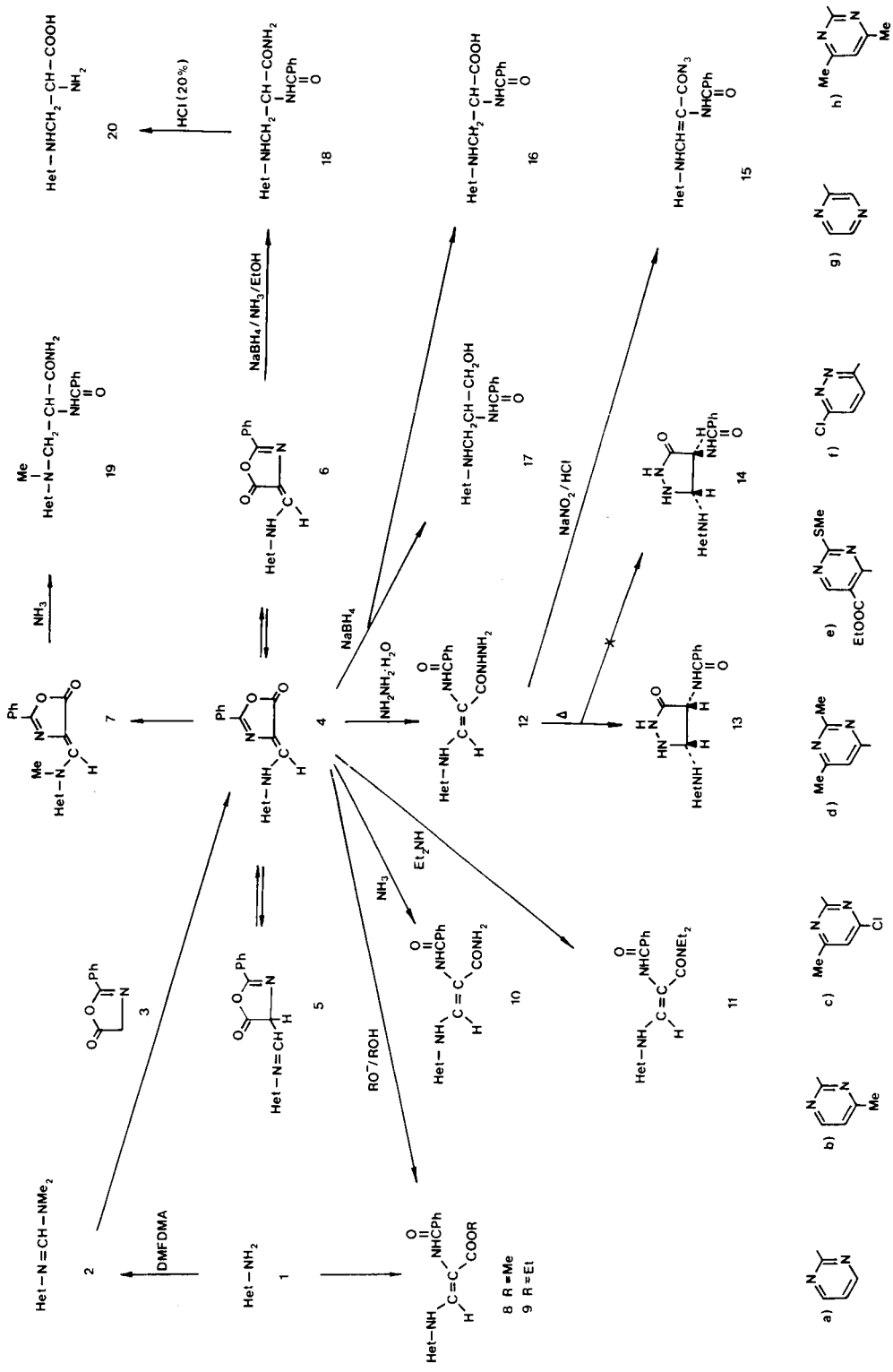
R_2 = H, Me

R_3 = alkyl, aryl, heteroaryl

In our preliminary communications we have reported on some novel methods, according to which derivatives of α-heteroaryl substituted α-amino acids and β-heteroarylamino-α,β-dehydro-α-amino acids can be obtained [5,6]. Since the transformations of *N*-heteroaryl-*N'*,*N'*-dimethylformamidines into esters of substituted β-amino-α,β-dehydro-α-amino acids are limited only to the primary amines, from which the corresponding formamidines can be obtained, another method has been developed in our laboratory, which can be applied to primary and secondary aliphatic, aromatic and heterocyclic amines [7].

We wish now to report the details of this general synthetic method and some further extensions. *N*-Heteroarylformamidines **2**, obtained from primary amines **1** and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) according to the known procedure [8,9] were converted with 2-phenyl-5-oxo-4,5-dihydro-1,3-oxazole (**3**) in the presence of acetic anhydride into the heteroarylaminomethyleneoxazolones, the intermediates which have been previously obtained in some instances from 4-alkoxymethylene- or 4-alkylthiomethylene-2-phenyl-5-oxo-4,5-dihydro-1,3-oxazoles and primary amines [10-12]. These compounds can exist in three tautomeric forms **4-6**. The structures were determined on the basis of the ^{1}H nmr spectra. Namely, two doublets at $\delta \cong$ 8.2-8.3 ppm and $\delta \cong$ 11 ppm with the coupling constants J = 12 Hz appear in nmr spectra in most cases. The doublets at the higher field are slightly broadened and disappear by the addition of deuterated water to the DMSO-d_6 solutions, while the doublets at lower are transformed into singlets. This clearly indicates that structures **4** or **6** exist in the solution. This is further supported by the selective methylation of **4b,c,d,f** with DMFDMA [13] producing the *N*-methylated compounds **7b,c,d,f** showing the *N*-methyl groups at δ = 4.02-4.18 ppm and the adjacent protons as singlets at δ = 8.12-8.80 ppm. The orientation around the C=C double bond was determined by X-ray analysis of **4h** showing that heteroarylamino group and nitrogen atom of the oxazolinone ring are oriented (*Z*) around the exocyclic C=C double bond [14].

The compounds **4** were converted with sodium methoxide in methanol or sodium ethoxide in ethanol into methyl esters **8d,e** and ethyl esters **9a-e**, respectively. The ^{1}H nmr spectra of these compounds, and the compounds which we have reported previously [6,7], show two doublets at δ = 8.18-8.25 ppm for CH and δ = 9.40-9.78 ppm for NH group with the coupling constant J_{CHNH} = 10-12 Hz. This indicates the *trans* orientation around the CH-NH bond. This is further supported by X-ray analysis, which also shows, to our surprise, that the orientation around the



Scheme 2

Table 1

Compound	Yield % mp °C	Solvent for recrystallization [a]	^{1}H NMR	δ (TMS) [b]
4b	63 246-247	washed with ethanol	DMSO-d_6 (90 MHz, 150°)	2.45 (s, 3H, 4'-Me), 7.03 (d, 1H, 5'-H), 7.51-7.58 (m, 3H, Ar), 7.94-8.06 (m, 2H, Ar), 8.28 (s, 1H, CH), 8.47 (d, 1H, 6'-H), $J_{5'\text{-H},6'\text{-H}}$ = 5.1 Hz
4d	40 230-232	ethanol water	DMSO-d_6	2.30 (s, 3H, 6'-Me), 2.46 (s, 3H, 2'-Me), 6.82 (s, 1H, 5'-H), 7.35-7.60 (m, 3H, Ar), 7.55-7.96 (m, 2H, Ar), 8.22 (s, 1H, C*H*-NH)
4e	72 199-203	toluene	$CDCl_3$	1.45 (t, 3H, *Me*CH_2), 2.55 (s, 3H, SMe), 4.40 (q, 2H, MeC*H*$_2$), 7.29-7.48 (m, 3H, Ar), 7.80-8.04 (m, 2H, Ar), 8.29 (d, 1H, C*H*NH), 8.73 (s, 1H, 6'-H), 11.08 (br d, 1H, CHN*H*), J_{MeCH_2} = 6.9 Hz, J_{CHNH} = 12.0 Hz
7b	86 219-221	1-propanol toluene	$CDCl_3$	2.45 (s, 3H, 4'-Me), 4.02 (s, 3H, N-Me), 6.77 (d, 1H, 5'-H), 7.27-7.50 (m, 3H, Ar), 7.84-8.06 (m, 2H, Ar), 8.32 (d, 1H, 6'-H), 8.80 (s, 1H, CH), $J_{5'\text{-H},6'\text{-H}}$ = 4.5 Hz
7c	93 239-241	1-propanol toluene	$CDCl_3$	2.46 (s, 3H, 6'-Me), 4.02 (s, 3H, N-Me), 6.80 (s, 1H, 5'-H), 7.31-7.52 (m, 3H, Ar), 7.87-8.05 (m, 2H, Ar), 8.67 (s, 1H, CH)
7d	80 239-240	1-propanol toluene	$CDCl_3$	2.45 (s, 3H, 6'-Me), 2.58 (s, 3H, 2'-Me), 3.90 (s, 3H, N-Me), 6.56 (s, 1H, 5'-H), 7.25-7.37 (m, 3H, Ar), 7.76-7.95 (m, 2H, Ar), 8.47 (s, 1H, CH)
7f	63 262-263	1-propanol toluene	$CDCl_3$ (90 MHz)	4.18 (s, 3H, N-Me), 7.43 (d, 1H, 5'-H), 7.47-7.54 (m, 3H, Ar), 7.57 (d, 1H, 4'-H), 8.02-8.13 (m, 2H, Ar), 8.12 (s, 1H, CH), $J_{4'\text{-H},5'\text{-H}}$ = 9.9 Hz
8d	85 196-199	ethanol water	$CDCl_3$ (90 MHz)	2.38 (s, 3H, 6'-Me), 2.60 (s, 3H, 2'-Me), 5.85 (s, 3H, OMe), 6.42 (s, 1H, 5'-H), 7.46-7.54 (m, 3H, Ar), 7.83-7.94 (m, 2H, Ph), 8.32 (d, 1H, C*H*NH), 8.43 (s, 1H, NHCO), 9.83 (d, 1H, CHN*H*), J_{CHNH} = 11.0 Hz
8e	81 167-170	ethanol	$CDCl_3$ (90 MHz)	Form 1: 1.32 (t, 3H, *Me*CH_2), 2.60 (s, 3H, SMe), 3.85 (s, 3H, OMe), 4.34 (q, 2H, MeC*H*$_2$), 7.47-7.55 (m, 3H, Ar), 7.80-8.00 (m, 3H, Ar, N*H*CO), 8.62 (d, 2H, C*H*NH), 8.81 (s, 1H, 6'-H), 10.71 (d, 1H, CHN*H*) Form 2: 1.40 (t, 3H, *Me*CH_2), 2.64 (s, 3H, SMe), 3.99 (s, 3H, OMe), 4.43 (q, 2H, MeC*H*$_2$), 7.47-7.55 (m, 3H, Ar), 7.80-8.00 (m, 3H, Ar, N*H*CO), 8.81 (s, 1H, 6'-H), 9.43 (d, 1H, C*H*NH), 12.07 (d, 1H, CHN*H*), J_{MeCH_2} = 7.0 Hz, J_{CHNH} = 11.6 Hz
9a	31 180-181 [c]	ethanol water	$CDCl_3$	1.36 (t, 3H, *Me*CH_2), 4.27 (q, 2H, MeC*H*$_2$), 6.73 (t, 1H, 5'-H), 7.26-7.56 (m, 3H, Ar), 7.66-7.96 (m, 2H, Ar), 8.21 (d, 1H, CH), 8.29 (br s, 1H, N*H*CO), 8.36 (d, 2H, 4'-H, 6'-H), 9.69 (br d, 1H, N*H*CH), J_{MeCH_2} = 6.9 Hz, $J_{4'\text{-H},5'\text{-H}}$ = $J_{5'\text{-H},6'\text{-H}}$ = 4.8 Hz, J_{NHCH} = 12 Hz
9b	91 193-196	2-propanol water	$CDCl_3$	1.36 (t, 3H, *Me*CH_2), 2.38 (s, 3H, 4'-Me), 4.26 (q, 2H, MeC*H*$_2$), 6.58 (d, 1H, 5'-H), 7.15-7.48 (m, 3H, Ar), 7.60-7.89 (m, 2H, Ar), 8.15 (br s, N*H*CH), 8.15 (d, 1H, 6'-H), 8.20 (d, 1H, NHC*H*), 9.40 (br d, 1H, N*H*CH), J_{MeCH_2} = 6.9 Hz, $J_{5'\text{-H},6'\text{-H}}$ = 4.9 Hz, J_{NHCH} = 12 Hz
9c	94 198-200	ethanol water	$CDCl_3$ (90 MHz)	1.38 (t, 3H, *Me*CH_2), 2.42 (s, 3H, 6'-Me), 4.33 (q, 2H, MeC*H*$_2$), 6.73 (s, 1H, 5'-H), 7.42-7.54 (m, 3H, Ar), 7.86-7.97 (m, 2H, Ar), 8.25 (d, 1H, NHC*H*), 8.32 (s, 1H, NHCO), 9.78 (d, 1H, N*H*CH), J_{MeCH_2} = 7.1 Hz, J_{NHCH} = 11.5 Hz
9d	42 193-195	ethanol water	$CDCl_3$	1.40 (t, 3H, *Me*CH_2), 2.36 (s, 3H, 6'-Me), 2.56 (s, 3H, 2'-Me), 4.28 (q, 2H, MeC*H*$_2$), 6.33 (s, 1H, 5'-H), 7.32-7.50 (m, 3H, Ar), 7.65-7.78 (m, 2H, Ar), 8.18 (d, 1H, NHC*H*), 8.28 (br s, 1H, NHCO), 9.70 (br d, N*H*CH), J_{MeCH_2} = 6.9 Hz, J_{NHCH} = 11.0 Hz
9e	74 157-160	ethanol	$CDCl_3$ (90 MHz)	Form 1: 1.38 (t, 3H, *Me*CH_2), 2.61 (s, 3H, S*Me*), 4.41 (q, 2H, MeC*H*$_2$), 7.42-7.58 (m, 3H, Ar), 7.79-8.07 (m, 3H, Ar and N*H*CO), 8.67 (d, 1H, C*H*NH), 8.82 (s, 1H, H_6), 10.80 (d, 1H, CHN*H*) Form 2: 1.38 (t, 3H, *Me*CH_2), 2.67 (s, 3H, SMe), 4.41 (q, 2H, MeC*H*$_2$), 7.42-7.58 (m, 3H, Ar), 7.79-8.07 (m, 3H, Ar and N*H*CO), 8.82 (s, 1H, H_6), 9.49 (d, 1H, C*H*NH), 12.06 (d, 1H, CHN*H*), J_{CHNH} = 11.7 Hz, J_{MeCH_2} = 7.0 Hz
10a	57 239-244	ethanol	DMSO-d_6	6.86 (t, 1H, 5'-H), 6.86 (s, 2H, NH_2), 7.39-7.54 (m, 3H, Ar), 7.86-8.02 (m, 2H, Ar), 8.10 (d, 1H, NHC*H*), 8.41 (d, 2H, 4'-H, 6'-H), 9.13 (s, 1H, NHCO), 9.33 (d, 1H, N*H*CH), $J_{4'\text{-H},5'\text{-H}}$ = $J_{5'\text{-H},6'\text{-H}}$ = 4.8 Hz, J_{CHNH} = 11.3 Hz
10b	58 246-250	2-propanol	DMSO-d_6 (90 MHz)	Form 1: 2.36 (s, 3H, 4'-Me), 6.84 (d, 1H, H_5), 6.96 (s, 2H, NH_2), 7.49-7.55 (m, 3H, Ar), 7.99-8.07 (m, 2H, Ar), 8.20 (d, 1H, C*H*NH), 8.36 (d, 1H, H_6), 9.12 (d, 1H, CHN*H*), 9.22 (s, 1H, NHCO) Form 2: 2.36 (s, 3H, 4'-Me), 6.84 (d, 1H, H_5), 7.20 (s, 2H, NH_2), 7.49-7.55 (m, 3H, Ar), 7.99-8.07 (m, 2H, Ar), 8.20 (d, 1H, C*H*NH), 9.44 (s, 1H, NHCO), 10.02 (d, 1H, CHN*H*), J_{CHNH} = 11.7 Hz, J_{H_5,H_6} = 4.9 Hz

Table 1 (continued)

Compound	Yield % mp °C	Solvent for recrystallization [a]	^{1}H NMR	δ (TMS) [b]
10c	34 217-219	methanol water	DMSO-d_6 (90 MHz)	Form 1: 2.37 (s, 3H, 6'-Me), 6.99 (s, 1H, $H_{5'}$), 7.01 (s, 2H, NH_2), 7.49-7.53 (m, 3H, Ar), 8.00-8.12 (m, 2H, Ar and d, 1H, C*H*NH), 9.20 (s, 1H, NHCO), 9.83 (d, 1H, C*H*NH) Form 2: 2.37 (s, 3H, 6'-Me), 6.99 (s, 1H, $H_{5'}$), 7.28 (s, 2H, NH_2), 7.49-7.53 (m, 3H, Ar), 8.00-8.12 (m, 2H, Ar and d, 1H, C*H*NH), 9.46 (s, 1H, NHCO), 11.19 (d, CHN*H*), J_{CHNH} = 11.1 Hz
10d	63 203-208	ethanol	DMSO-d_6 (90 MHz)	2.36 (s, 3H, 6'-Me), 2.45 (s, 3H, 2'-Me), 6.65 (s, 1H, 5'-H), 7.00 (s, 2H, NH_2), 7.55 (m, 3H, Ar), 8.00-8.09 (m, 2H, Ar), 8.30 (d, 1H, NHC*H*), 9.23 (d, 1H, N*H*CH), 9.29 (s, 1H, NHCO), J_{NHCH} = 11.0 Hz
10e	56 187-189	2-propanol	DMSO-d_6 (90 MHz)	1.31 (t, 3H, *Me*CH_2), 2.48 (s, 3H, SMe), 4.36 (q, 2H, MeCH_2), 7.20-7.99 (m, 10H, Ar, NH_2, NH,NH,CH, J_{MeCH_2} = 7.0 Hz
10g	67 197-200	methanol	DMSO-d_6 (90 MHz)	6.65 (s, 2H, NH_2), 7.47-7.54 (m, 3H, Ar), 7.98-9.04 (m, 5H, Ar, 3'-H, 5'-H, 6'-H)
10h	71 247-250	benzene ethanol	DMSO-d_6 (90 MHz)	Form 1: 2.31 (s, 6H, 4'-Me, 6'-Me), 6.72 (s, 1H, $H_{5'}$), 6.93 (s, 2H, NH_2), 7.47-7.55 (m, 3H, Ar), 7.98-8.09 (m, 2H, Ar), 8.20 (d, 1H, CHN*H*), 9.17 (d, 1H, C*H*NH), 9.18 (s, 1H, NHCO) Form 2: 2.31 (s, 6H, 4'-Me, 6'-Me), 6.75 (s, 1H, $H_{5'}$), 7.17 (s, 2H, NH_2), 7.47-7.55 (m, 3H, Ar), 7.98-8.08 (m, 2H, Ar), 8.20 (d, 1H, C*H*NH), 9.41 (s, 1H, NHCO), 10.91 (d, 1H, CHN*H*), J_{CHNH} = 11.90 Hz
11a	61 170-173	ethanol water	$CDCl_3$	1.25 (t, 3H, *Me*CH_2), 3.49 (q, 2H, Me*CH*$_2$), 6.62 (t, 1H, 5'-H), 7.25-7.49 (m, 3H, Ar, d, 1H, *CH*NH), 7.72-7.91 (m, 2H, Ar), 8.23 (d, 2H, 4'-H, 6'-H), 8.51 (br d, 1H, CHN*H*), 8.96 (br s, 1H, N*H*CO), J_{MeCH_2} = 6.9 Hz, $J_{4'-H,5'-H}$ = $J_{5'-H,6'-H}$ = 4.8 Hz, J_{CHNH} = 10.5 Hz
11b	35 125-130	methanol water	$CDCl_3$ (90 MHz)	1.26 (t, 3H, *Me*CH_2), 2.37 (s, 3H, 4'-CH_3), 3.55 (q, 2H, MeC*H*$_2$), 6.63 (d, 1H, 5'-H), 7.40-7.65 (m, 3H, Ar and d, 1H, C*H*NH), 7.90-7.99 (m, 2H, Ar), 8.23 (d, 1H, 6'-H), 8.62 (d, 1H, CHN*H*), 9.03 (s, 1H, NHCO), J_{MeCH_2} = 7.0 Hz, $J_{5'-H,6'-H}$ = 5.0 Hz, J_{CHNH} = 11.4 Hz
11c	39 118-120	ethanol water	$CDCl_3$	1.25 (t, 3H, MeCH_2), 2.27 (s, 3H, 6'-Me), 3.50 (q, 2H, MeC*H*$_2$), 6.52 (s, 1H, 5'-H), 7.21-7.40 (m, 3H, Ar, and d, 1H, C*H*NH), 7.73-7.90 (m, 2H, Ar), 8.43 (br d, 1H, CHN*H*), 9.13 (br s, NHCO), J_{MeCH_2} = 6.9 Hz, J_{CHNH} = 10.5 Hz
11d	67 117-121	*n*-heptane CCl_4	$CDCl_3$	1.26 (t, 3H, MeCH_2), 2.29 (s, 3H, 6'-Me), 2.45 (s, 3H, 2'-Me), 3.50 (q, 2H, MeC*H*$_2$), 6.18 (s, 1H, 5'-H), 7.27-7.54 (m, 3H, Ar, and d, 1H, C*H*NH), 7.70-7.87 (m, 2H, Ar), 8.73 (br d, 1H, CHN*H*), 9.03 (br s, 1H, NHCO), J_{MeCH_2} = 6.9 Hz, J_{CHNH} = 10.5 Hz
11f	35 167-169	methanol	$CDCl_3$ (90 MHz)	1.23 (t, 3H, *Me*CH_2), 3.52 (q, 2H, MeC*H*$_2$), 6.96 (d, 1H, 5'-H), 7.23 (d, 1H, 4'-H), 7.38-7.61 (m, 3H, Ar, and d, 1H, C*H*NH), 7.83-7.94 (m, 2H, Ar), 9.24 (d, 1H, CHN*H*), 9.28 (s, 1H, NHCO), J_{MeCH_2} = 7.1 Hz, $J_{4'-H,5'-H}$ = 9.2 Hz, J_{CHNH} = 10.5 Hz
11g	60 200-203	methanol water	$CDCl_3$	1.26 (t, 3H, *Me*CH_2), 3.52 (q, 2H, Me*CH*$_2$), 7.13-7.47 (m, 3H, Ar, and d, 1H, C*H*NH), 7.75-8.09 (m, 5H, Ar, 3'-H, 5'-H, 6'-H), 8.96 (br d, 1H, CHN*H*), 9.04 (br s, 1H, NHCO), J_{MeCH_2} = 6.9 Hz, J_{CHNH} = 10.5 Hz
12c	92 247-250	ethanol	DMSO-d_6 (90 MHz)	2.37 (s, 3H, 6'-Me), 4.29 (s, 2H, NH_2), 6.99 (s, 1H, 5'-H), 7.37-7.58 (m, 3H, Ar), 7.94-8.07 (m, 2H, Ar), 8.0 (d, 1H, NHC*H*), 8.96 (s, 1H, NHCO), 9.13 (s, 1H, NHCO), 9.83 (d, 1H, N*H*CH), J_{NHCH} = 11.6 Hz
12d	55 185-190	ethanol	DMSO-d_6 (90 MHz)	2.25 (s, 3H, 6'-Me), 2.44 (s, 3H, 2'-Me), 4.27 (s, 2H, NH_2), 6.63 (s, 1H, 5'-H), 7.53-7.58 (m, 3H, Ar), 7.99-8.08 (m, 2H, Ar), 8.22 (d, 1H, NHC*H*), 8.93 (s, 1H, NHCO), 9.18 (d, 1H, N*H*CH), 9.24 (s, 1H, NHCO)
12e	72 205-208	ethanol	DMSO-d_6	1.19 (t, 3H, *Me*CH_2), 2.52 (s, 3H, SMe), 4.16 (q, 2H, MeC*H*$_2$), 4.27 (s, 2H, NH_2), 7.32-7.43 (m, 3H, Ar), 7.80-7.99 (m, 2H, Ar), 8.08 (d, 1H, NHC*H*), 8.57 (s, 1H, 6'-H), 9.18 (s, 1H, NHCO), 9.41 (s, 1H, NHCO), 9.85 (d, 1H, N*H*CH), J_{MeCH_2} = 6.8 Hz, J_{NHCH} = 11.5 Hz
12f	65 165-168	ethanol	DMSO-d_6 (90 MHz)	4.26 (s, 2H, NH_2), 7.36 (d, 1H, 5'-H), 7.48-7.58 (m, 3H, Ar), 7.63 (d, 1H, 4'-H), 8.00-8.09 (m, 2H, Ar), 8.26 (d, 1H, NHC*H*), 8.96 (s, 1H, NHCO), 9.18 (d, 1H, N*H*CH), 9.23 (s, 1H, NHCO), $J_{4'-H,5'-H}$ = 9.4 Hz, J_{NHCH} = 11.5 Hz

Table 1 (continued)

Compound	Yield % mp °C	Solvent for recrystallization [a]	^{1}H NMR	δ (TMS) [b]
13a	46 206-210	ethanol	DMSO-d_6 (90 MHz)	5.15 (dd, 1H, 4'-H), 5.58 (m, 1H, 3'-H), 5.90 (d, 1H, 2'-H), 6.68 (t, 1H, 5''-H), 7.44-7.65 (m, 4H, Ar, HetN*H*), 7.82-8.06 (m, 2H, Ar), 8.31 (d, 2H, 4''-H, 6''-H), 8.45 (d, 1H, CHN*H*COAr), 9.43 (s, 1H, NH), $J_{4''\text{-}H,5''\text{-}H}$ = $J_{5''\text{-}H,6''\text{-}H}$ = 4.7 Hz, $J_{2'\text{-}H,3'\text{-}H}$ = 3.4 Hz, $J_{3'\text{-}H,4'\text{-}H}$ = 8.5 Hz, $J_{4'\text{-}H,NHCO}$ = 8.5 Hz
13g	61 186-190	ethanol	DMSO-d_6 (90 MHz)	5.19 (dd, 1H, 4'-H), 5.59 (ddd, 1H, 3'H), 5.91 (d, 1H, 2'-H), 7.44-7.57 (m, 4H, Ar, HetN*H*), 7.72-7.99 (m, 5H, Ar, 3''-H, 5''-H, 6''-H), 8.33 (d, 1H, NHCOPh), 9.49 (s, 1H, NH), $J_{3'\text{-}H,4'\text{-}H}$ = 7.7 Hz, $J_{2'\text{-}H,3'\text{-}H}$ = 3.4 Hz, $J_{4'\text{-}H,NHCOPh}$ = 8.8 Hz
15c	65 135-140	washed with water and ether	DMSO-d_6 (90 MHz)	2.42 (s, 3H, 6'-Me), 7.17 (s, 1H, 5'-H), 7.56 (m, 3H, Ar), 7.95-8.04 (m, 2H, Ar), 8.46 (d, 1H, C*H*NH), 9.33 (s, 1H, NHCO), 10.81 (d, 1H, CHN*H*), J_{CHNH} = 12.3 Hz
17a	63 177-180	ethanol water	DMSO-d_6 (90 MHz)	3.53-3.72 (m, 4H, CH_2-CH-CH_2), 4.10-4.15 (m, 1H, CH), 4.88 (br s, 1H, N*H*CH_2), 6.57 (t, 1H, 5'-H), 7.13 (t, 1H, O*H*), 7.50-7.52 (m, 3H, Ar), 7.81-7.90 (m, 2H, Ar), 8.15 (d, 1H, NHCO), 8.28 (d, 2H, 4'-H,6'-H), $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 4.6 Hz
17b	82 163-164	methanol water	DMSO-d_6 (90 MHz)	2.22 (s, 3H, 4'-Me), 3.52-3.59 (m, 4H, CH_2CHCH_2), 4.14-4.27 (m, 1H, C*H*), 4.83 (t, 1H, N*H*CH_2), 6.46 (d, 1H, 5'-H), 6.99 (br s, 1H, OH), 7.43-7.51 (m, 3H, Ar), 7.78-7.89 (m, 2H, Ar), 8.13 (m, 2H, 6'-H, NHCO), $J_{5'\text{-}H,6'\text{-}H}$ = 5.1 Hz, J_{NHCH_2} = 6.0 Hz, J_{NHCH} = 5.6 Hz
17c	57 186-187	2-propanol	DMSO-d_6 (90 MHz)	2.34 (s, 3H, 6'-Me), 3.63-3.78 (m, 4H, CH_2CHCH_2), 4.18 (m, 1H, C*H*), 6.25 (br t, 1H, N*H*CH_2), 6.52 (s, 1H, 5'-H), 7.12 (br d, 1H, NHCO), 7.33-7.47 (m, 3H, Ar), 7.56-7.86 (m, 2H, Ar), J_{NHCH_2} = J_{NHCH} = 7.0 Hz
17d	95 198-200	ethanol water	DMSO-d_6 (90 MHz)	2.15 (s, 3H, 6'-Me), 2.59 (s, 3H, 2'-Me), 3.50 (br s, 4H, CH_2-CH-CH_2), 4.03-4.26 (m, 1H, C*H*), 4.99 (br s, 1H, N*H*CH_2), 6.22 (s, 1H, 5'-H), 7.19 (br t, 1H, O*H*), 7.43-7.51 (m, 3H, Ar), 7.80-7.91 (m, 2H, Ar), 8.18 (d, 1H, N*H*CH), J_{NHCH} = 7.6 Hz
17e	58 180-183	methanol water	DMSO-d_6 (90 MHz)	1.26 (t, 3H, *Me*CH_2), 2.49 (s, 3H, SMe), 3.55 (m, 2H, CH_2), 4.24 (q, 2H, MeCH_2 and m, 3H, CH,CH_2), 4.95 (t, N*H*CH_2), 7.43-7.51 (m, 3H, Ar), 7.76-7.87 (m, 2H, Ar), 8.23 (d, 1H, CHN*H*), 8.47 (br t, 1H, OH), 8.53 (s, 1H, H_6), J_{MeCH_2} = 7.0 Hz, J_{CH_2NH} = 5.6 Hz, J_{CHNH} = 7.0 Hz
17f	77 187-189	methanol water	DMSO-d_6 (90 MHz)	3.55-3.61 (m, 4H, CH_2CHCH_2), 4.23 (m, 1H, C*H*), 4.87 (t, 1H, N*H*CH_2), 6.97 (d, 1H, 5'-H), 7.18 (t, 1H, O*H*), 7.36 (d, 1H, 4'-H), 7.42-7.51 (m, 3H, Ar), 7.80-7.91 (m, 2H, Ar), 8.22 (d, 1H, NHCH), $J_{4'\text{-}H,5'\text{-}H}$ = 9.4 Hz, J_{NHCH_2} = 5.7 Hz, J_{NHCH} = 7.8 Hz
17g	53 189-191	methanol water	DMSO-d_6 (90 MHz)	3.50-3.56 (m, 4H, CH_2CHCH_2), 4.04-4.41 (m, 1H, C*H*), 4.85 (t, 1H, N*H*CH_2), 7.11 (t, 1H, O*H*), 7.45-7.98 (m, 8H, Ar, 3'-H,5'-H,6'-H), 8.18 (d, 1H, N*H*CH), J_{NHCH} = 5.6 Hz, J_{NHCH_2} = 6.0 Hz, J_{CH_2OH} = 6.0 Hz
18a	36 230-233	ethanol	DMSO-d_6 (90 MHz)	3.47-3.80 (m, 2H, CH_2), 4.65 (m, 1H, C*H*), 6.61 (t, 1H, 5'-H), 7.16-7.22 (br s, 2H, NH_2), 7.46-7.54 (m, 4H, Ar, N*H*CH_2), 7.84-7.95 (m, 2H, Ar), 8.31 (d, 2H, 4'-H, 6'-H), 8.58 (d, 1H, N*H*CH), $J_{4'\text{-}H,5'\text{-}H}$ = $J_{5'\text{-}H,6'\text{-}H}$ = 4.8 Hz, J_{NHCH} = 7.1 Hz
18b	74 236-240	ethanol DMF	DMSO-d_6 (90 MHz)	2.24 (s, 3H, 4'-Me), 3.54-3.93 (m, 2H, CH_2), 4.60-4.65 (m, 1H, NHC*H*), 6.55 (d, 1H, 5'-H), 7.18 (br s, NH_2), 7.40-7.56 (m, 3H, Ar), 7.82-7.99 (m, 2H, Ar), 8.16 (d, 1H, 6'-H), 8.57 (d, N*H*CH), $J_{5'\text{-}H,6'\text{-}H}$ = 5.0 Hz, J_{NHCH} = 7.6 Hz
18c	55 257-259	ethanol DMF	DMSO-d_6 (90 MHz)	2.23 (s, 3H, 6'-Me), 3.72-3.79 (dd, 1H, CH_2), 4.60-4.74 (dd, 1H, CH), 6.53 (s, 1H, 5'-H), 7.34-7.52 (m, 3H, Ar), 7.78-7.89 (m, 2H, Ar), J_{CH_2CH} = 6.8 Hz
18d	42 248-250	methanol water	DMSO-d_6 (90 MHz)	2.15 (s, 3H, 6'-Me), 2.29 (s, 3H, 2'-Me), 3.72 (m, 2H, CH_2), 4.51-4.73 (m, 1H, C*H*), 6.19 (s, 1H, 5'-H), 6.69 (br t, 1H, N*H*CH_2), 6.94 (br s, 2H, NH_2), 7.35-7.54 (m, 3H, Ar), 7.75-7.86 (m, 2H, Ar), 8.14 (br d, 1H, NHCO), J_{CH_2CH} = 6.5 Hz, J_{NHCH} = 7.0 Hz
18e	49 207-208	ethanol DMF	DMSO-d_6 (90 MHz)	1.26 (t, 3H, *Me*CH_2), 2.50 (s, 3H, S Me), 3.54-3.86 (m, 1H, CH_2), 4.25 (q, 2H, MeCH_2, m, 1H, CH_2), 4.52-4.78 (m, 1H, C*H*), 7.21 (s, 2H, NH_2), 7.45-7.56 (m, 3H, Ar), 7.82-7.93 (m, 2H, Ar), 8.54 (s, 1H, 6'-H), 8.57 (t, 1H, N*H*CH_2), 8.62 (d, 1H, NHCO), J_{MeCH_2} = 7.1 Hz, J_{NHCH} = 7.8 Hz

Table 1 (continued)

Compound	Yield % mp °C	Solvent for recrystallization [a]	^{1}H NMR	δ (TMS) [b]
18f	60 211-213	ethanol DMF	DMSO-d_6 (90 MHz)	3.68-3.84 (m, 2H, CH_2), 4.57-4.80 (m, 1H, C*H*), 6.98 (d, 1H, 5'-H), 7.18-7.24 (br s, 2H, NH_2), 7.38 (d, 1H, 4'-H), 7.44-7.56 (m, 4H, Ar, N*H*CH_2), 7.84-7.95 (m, 2H, Ar), 8.65 (d, 1H, N*H*CH), $J_{4'\text{-}H,5'\text{-}H}$ = 9.3 Hz, J_{NHCH} = 7.6 Hz
18g	39 203-205	methanol water	DMSO-d_6 (90 MHz)	3.63-3.80 (m, 2H, CH_2), 4.60-4.68 (m, 1H, C*H*), 7.20 (s, 2H, NH_2), 7.46-7.54 (m, 3H, Ar), 7.70 (d, 1H, 3'-H), 7.84-8.02 (m, 4H, Ar, 5'-H,6'-H), 8.59 (d, 1H, NHCO), $J_{3'\text{-}H,5'\text{-}H}$ = 2.70 Hz, J_{NHCH} = 7.6 Hz
18h	68 237-238	ethanol DMF	DMSO-d_6	2.15 (s, 6H, 4'-Me, 6'-Me), 3.65 (dd, 2H, CH_2), 4.50 (m, 1H, C*H*), 6.21 (s, 1H, 5'-H), 6.50 (br t, 1H, N*H*CH_2), 6.88 (br s, 2H, NH_2), 7.15-7.45 (m, 3H, Ar), 7.55-7.80 (m, 2H, Ar), 8.10 (br d, 1H, N*H*CH), J_{CH_2CH} = 6.3 Hz, J_{NHCH} = 7.0 Hz
19f	23 215-217	methanol water	DMSO-d_6 (90 MHz)	3.10 (s, 3H, N-Me), 3.96 (d, 2H, CH_2), 4.91 (dd, 1H, C*H*), 7.19-7.90 (m, 7H, Ar, 4'-H,5'-H), 8.57 (d, 1H, N*H*CH), J_{CH_2CH} = 7.1 Hz, J_{NHCH} = 8.5 Hz
19h	41 225-228	water	DMSO-d_6 (90 MHz)	2.31 (s, 6H, 4'-Me, 6'-Me), 3.26 (s, 3H, N-Me), 3.51-3.62 (m, 2H, CH_2), 3.93-4.41 (m, 1H, C*H*), (2H, NH_2), 6.33 (s, 1H, 5'-H), 7.28 (br d, 1H, N*H*CH), 7.47-7.52 (m, 3H, Ar), 7.76-7.85 (m, 2H, Ar), J_{NHCH} = 7.2 Hz

[a] The yields of purified products are given. [b] The ^{1}H nmr spectra were recorded at 60 MHz unless otherwise stated. [c] Lit [11] mp 181-182.

Table 2

Product	Molecular formula		Analyses C	H	N
4b	$C_{15}H_{12}N_4O_2$	Calcd.	64.28	4.32	19.99
		Found	64.32	4.48	19.87
4d	$C_{16}H_{14}N_4O_2$	Calcd.	65.30	4.79	19.04
		Found	65.28	4.89	19.22
4e	$C_{18}H_{16}N_4O_4S$	Calcd.	56.24	4.20	14.57
		Found	56.26	4.25	14.41
7b	$C_{16}H_{14}N_4O_2$	Calcd.	65.30	4.79	19.04
		Found	65.08	4.88	19.05
7c	$C_{16}H_{13}ClN_4O_2$	Calcd.	58.46	3.99	17.04
		Found	58.37	3.92	17.06
7d	$C_{17}H_{16}N_4O_2$	Calcd.	66.22	5.23	18.17
		Found	66.25	5.37	18.05
7f	$C_{15}H_{11}ClN_4O_2$	Calcd.	57.24	3.52	17.80
		Found	57.21	3.47	17.80
8d	$C_{17}H_{18}N_4O_3$	Calcd.	62.56	5.56	17.17
		Found	62.71	5.64	17.04
8e	$C_{19}H_{20}N_4O_5S$	Calcd.	54.80	4.84	13.45
		Found	54.64	4.84	13.52
9a	$C_{16}H_{16}N_4O_3$	Calcd.	61.53	5.16	17.94
		Found	61.31	5.16	17.79
9b	$C_{17}H_{18}N_4O_3$	Calcd.	62.56	5.56	17.17
		Found	62.40	5.77	16.97
9c	$C_{17}H_{17}ClN_4O_3$	Calcd.	56.59	4.75	15.53
		Found	56.49	4.80	15.35
9d	$C_{18}H_{20}N_4O_3$	Calcd.	63.52	5.92	16.46
		Found	63.66	5.92	16.51
9e	$C_{20}H_{22}N_4O_5S$	Calcd.	55.80	5.15	13.01
		Found	55.69	4.93	13.25
10a	$C_{14}H_{13}N_5O_2$	Calcd.	59.36	4.63	24.72
		Found	59.09	4.69	24.56
10b	$C_{15}H_{15}N_5O_2$	Calcd.	60.60	5.09	23.56
		Found	60.43	5.39	23.65
10c	$C_{15}H_{14}ClN_5O_2$	Calcd.	54.31	4.25	21.11
		Found	54.23	4.36	21.00
10d	$C_{16}H_{17}N_5O_2$	Calcd.	61.72	5.50	22.49
		Found	61.51	5.60	22.44
10e	$C_{18}H_{19}N_5O_4S$	Calcd.	53.85	4.77	17.45
		Found	54.03	5.02	17.21
10g	$C_{14}H_{13}N_5O_2$	Calcd.	59.36	4.63	24.72
		Found	59.33	4.52	24.33
10h	$C_{16}H_{17}N_5O_2$	Calcd.	61.72	5.50	22.49
		Found	62.01	5.43	22.64
11a	$C_{16}H_{21}N_5O_2$	Calcd.	63.70	6.24	20.63
		Found	63.68	6.38	20.40
11b	$C_{19}H_{23}N_5O_2$	Calcd.	64.57	6.56	19.82
		Found	64.43	6.73	19.70
11c	$C_{19}H_{22}ClN_5O_2$	Calcd.	58.84	5.72	18.06
		Found	58.61	5.68	17.90
11d	$C_{20}H_{25}N_5O_2$	Calcd.	65.37	6.86	19.06
		Found	65.27	6.86	18.89
11f	$C_{18}H_{20}ClN_5O_2$	Calcd.	57.83	5.39	18.73
		Found	57.64	5.50	18.85
11g	$C_{18}H_{21}N_5O_2$	Calcd.	63.70	6.24	20.63
		Found	63.80	6.48	20.48
12c	$C_{15}H_{11}ClN_6O_2$	Calcd.	51.95	4.36	24.23
		Found	51.90	4.53	24.08
12d	$C_{16}H_{18}N_6O_2$	Calcd.	58.89	5.56	25.75
		Found	58.64	5.62	25.57
12e	$C_{18}H_{20}N_6O_4S$	Calcd.	51.91	4.84	20.18
		Found	51.90	4.79	20.16
12f	$C_{14}H_{13}ClN_6O_2$	Calcd.	50.53	3.94	25.26
		Found	50.54	3.94	24.97
13a	$C_{14}H_{14}N_6O_2$	Calcd.	56.37	4.73	28.17
		Found	56.34	4.73	28.02
13g	$C_{14}H_{14}N_6O_2$	Calcd.	56.37	4.73	28.17
		Found	56.69	4.87	28.28
15c	$C_{15}H_{12}ClN_7O_2$	Calcd.	50.36	3.38	27.41
		Found	50.57	3.45	27.14
17a	$C_{14}H_{16}N_4O_2$	Calcd.	61.75	5.92	20.57
		Found	61.91	5.84	20.27
17b	$C_{15}H_{18}N_4O_2$	Calcd.	62.92	6.34	19.57
		Found	62.78	6.43	19.53
17c	$C_{15}H_{17}ClN_4O_2$	Calcd.	56.17	5.34	17.47
		Found	56.31	5.34	17.39

Table 2 (continued)

Product	Molecular formula		Analyses C	H	N
17d	$C_{16}H_{20}N_4O_2$	Calcd.	63.98	6.71	18.65
		Found	64.10	6.66	19.00
17e	$C_{16}H_{22}N_4O_4S$	Calcd.	55.37	5.68	14.35
		Found	55.61	5.71	14.34
17f	$C_{14}H_{15}ClN_4O_2$	Calcd.	54.82	4.93	18.26
		Found	54.83	4.94	18.01
17g	$C_{14}H_{16}N_4O_2$	Calcd.	61.75	5.92	20.57
		Found	61.54	5.93	20.26
18a	$C_{14}H_{15}N_5O_2$	Calcd.	58.94	5.30	24.55
		Found	58.98	5.08	24.31
18b	$C_{15}H_{17}N_5O_2$	Calcd.	60.19	5.72	23.40
		Found	60.28	5.76	23.38
18c	$C_{15}H_{16}ClN_5O_2$	Calcd.	53.98	4.83	20.98
		Found	53.90	5.01	20.94
18d	$C_{16}H_{19}N_5O_2$	Calcd.	61.33	6.11	22.35
		Found	61.02	6.22	22.15
18e	$C_{16}H_{21}N_5O_2S$	Calcd.	53.59	5.25	17.36
		Found	53.47	5.25	17.50
18f	$C_{14}H_{14}ClN_5O_2$	Calcd.	52.59	4.41	21.90
		Found	52.62	4.56	21.76
18g	$C_{14}H_{15}N_5O_2$	Calcd.	58.94	5.30	24.55
		Found	59.08	5.34	24.30
18h	$C_{16}H_{19}N_5O_2$	Calcd.	61.33	6.11	22.35
		Found	61.59	6.21	22.11
19f	$C_{15}H_{16}ClN_5O_2$	Calcd.	53.97	4.83	20.98
		Found	54.06	4.90	20.85
19h	$C_{17}H_{21}N_5O_2$	Calcd.	62.37	6.47	21.39
		Found	62.54	6.67	21.16

C=C double bond is (*Z*) [14]. However, the only exceptions are the esters **8e** and **9e**, which show two sets of signals in the ^{1}H nmr spectra, indicating that the equilibrium between (*Z*)- and (*E*)-isomers exists in the solution most probably due to the steric hindrance of the substituted pyrimidine ring.

The oxazolinone derivatives **4** were converted with ammonia into the corresponding amides **10e,g,h**, and with diethylamine the corresponding diethylamides **11a-f,g** were obtained. In the reaction of **4c-f** with hydrazine hydrate at room temperature the hydrazides **12c-f** were formed in some instances. However, the oxazolinone derivatives **4a,g** remained under these conditions unchanged, while at elevated temperatures (80°) the cyclization occurred to give pyrazoline derivatives **13a,g** or **14a,g**. The large coupling constants between H_3 and H_4, J = 7.7-8.5 Hz, in pyrazolinone ring, similar to those observed in other derivatives [15], indicate that both protons are *cis* to each other. This eliminates the structures **14a,g**. The hydrazide **12c** gave by treatment with nitrous acid the azide **15c**.

The amides **10** and **11** and hydrazides **12** were isolated only in one form. However, for the amides **10b,c,h** two sets of peaks were observed in the ^{1}H nmr spectra in DMSO-d_6 solutions, showing thus that the equilibrium between (*Z*)- and (*E*)-isomers exist in these examples. On the basis of cyclization of **4a,g** *via* **12a,g** into **13a,g** in the presence of hydrazine reported in this paper, and on the basis of the structure of a dipeptide prepared previously from the hydrazide **12h** *via* the azide **15h** [6], for which the (*Z*) orientation around the C=C double bond was shown by X-ray analysis [14], we believe that all these compounds exist in (*Z*)-form. We reported earlier that reduction of the C=C double bond with sodium borohydride the oxazolinone derivative **4h** produced the saturated α-amino acid derivative **16h**. However, this selective reduction is an extremely delicate procedure, which is usually accompanied also with the reduction of the ester group producing the hydroxy derivatives **17a-g**. In order to overcome these difficulties another procedure was developed. The oxazolones **4a-h** were treated with sodium borohydride in ethanol saturated with ammonia. Under these conditions the C=C double bond was selectively reduced and oxazolinone ring opened to give the amides of the saturated acids **18a-h**. The compound **18h** was obtained from **4h** also by catalytic hydrogenation over Raney nickel in a mixture of ethanol and aqueous ammonia. Similarly, the *N*-methyl substituted oxazolones **7f,h** produced the *N*-methyl substituted saturated amides **19f,h**. When compounds **18c,f,h** were treated with hydrochloric acid (20%), the hydrolysis of both the amide and the benzoylamino group took place to give β-heteroarylamino-α-amino acids **20c,f,h**.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a JEOL C 60 HL or 90Q FT spectrometer with TMS as internal standard and elemental analyses for C, H, and N on a Perkin-Elmer CHN Analyser 240 C.

N-Heteroarylformamidines **2** were prepared from the corresponding amino compounds **1** and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) according to the general procedure described previously [8,9].

The following compounds were prepared according to the procedures we have described previously [6,7]: 2-phenyl-4-(2-pyrimidinylamino)-methylene-5(4*H*)-oxazolone (**4a**), 2-phenyl-4-(4-chloro-6-methyl-2-pyrimidinylamino)methylene-5(4*H*)-oxazolone (**4c**), 2-phenyl-4-(6-chloro-3-pyridazinylamino)methylene-5(4*H*)-oxazolone (**4f**), 2-phenyl-4-(2-pyrazinylamino)methylene-5(4*H*)-oxazolone (**4g**), 2-phenyl-4-(4,6-dimethyl-2-pyrimidinylamino)methylene-5(4*H*)-oxazolone (**4h**), and 2-phenyl-4-[*N*-methyl-(4,6-dimethyl-2-pyrimidinyl)amino]methylene-5(4*H*)-oxazolone (**7h**).

2-Phenyl-4-heteroarylaminomethylene-5(4*H*)-oxazolones **4**.

According to the procedure we have described previously for **4h** [6,7] the following compounds were prepared: 2-Phenyl-4-(4-methyl-2-pyrimidinylamino)methylene-4(5*H*)oxazolone (**4b**) and 2-phenyl-4-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinylamino)methylene-5(4*H*)-oxazolone (**4e**). The experimental and analytical data are summarized in Tables 1 and 2.

2-Phenyl-4-(*N*-methyl-*N*-heteroaryl)aminomethylene-5(4*H*)-oxazolones **7**.

According to the procedure we have described previously for **7h** [6] the following compounds were prepared: 2-Phenyl-4-[*N*-methyl(4-methyl-2-

pyrimidinyl)amino]methylene-5(4*H*)-oxazolone (**7b**), 2-phenyl-4-[*N*-methyl(chloro-6-methyl-2-pyrimidinyl)amino]methylene-5(4*H*)oxazolone (**7c**), 2-phenyl-4-[*N*-methyl(2,6-dimethyl-4-pyrimidinyl)amino]methylene-5(4*H*)-oxazolone (**7d**), and 2-phenyl-4-[*N*-methyl-(6-chloro-3-pyridazinyl)-amino]methylene-5(4*H*)-oxazolone (**7f**). The experimental and analytical data are summarized in Tables 1 and 2.

Methyl (*Z*)-2-Benzoylamino-3-heteroarylaminopropenoates **8**.

The following compounds were prepared according to the procedure we have described previously for other derivatives [7]: Methyl (*Z*)-2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropenoate (**8d**), and methyl (*Z*)-2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)aminopropenoate (**8e**). The experimental and analytical details are summarized in Tables 1 and 2.

Ethyl (*Z*)-2-Benzoylamino-3-heteroarylaminopropenoates **9**. General Procedure.

A mixture of **4** (0.001 mole) and triethylamine (0.5 ml) in ethanol (5 ml) was heated under reflux (2-10 hours). The precipitate was, after cooling, filtered to give crude product. The filtrate was evaporated *in vacuo*, water (10 ml) was added to the residue and the precipitate was filtered. The combined solids were recrystallized from an appropriate solvent to give **9**.

In this manner the following compounds were prepared: Ethyl (*Z*)-2-benzoylamino-3-(2-pyrimidinyl)aminopropenoate (**9a**), ethyl (*Z*)-2-benzoylamino-3-(4-methyl-2-pyrimidinyl)aminopropenoate (**9b**), ethyl (*Z*)-2-benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropenoate (**9c**), ethyl (*Z*)-2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropenoate (**9d**), and ethyl (*Z*)-2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)aminopropenoate (**9e**). The experimental and analytical data are summarized in Tables 1 and 2.

(*Z*)-2-Benzoylamino-3-heteroarylaminopropenamides **10**. General Procedure.

A mixture of **4** (0.001 mole) and liquid ammonia (10 ml) was left in an autoclave at room temperature (10 hours). Ammonia was then evaporated at room temperature and the solid residue was dissolved in methanol (10 ml). The product was precipitated by the addition of ice-cold water and the crude product recrystallized from an appropriate solvent. In this manner the following compounds were prepared: (*Z*)-2-Benzoylamino-3-(2-pyrimidinyl)aminopropenamide (**10a**), (*Z*)-2-benzoylamino-3-(4-methyl-2-pyrimidinyl)aminopropenamide (**10b**), (*Z*)-2-benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropenamide (**10c**), (*Z*)-2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropenamide (**10d**), (*Z*)-2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)aminopropenamide (**10e**), (*Z*)-2-benzoylamino-3-(2-pyrazinyl)aminopropenamide (**10g**), and (*Z*)-2-benzoylamino-3-(4,6-dimethyl-2-pyrimidinyl)aminopropenamide (**10h**). The experimental and analytical details are summarized in Tables 1 and 2.

N,N-Diethyl (*Z*)-2-Benzoylamino-3-heteroarylaminopropenamides **11**.

According to the procedure we have described previously for **11h** [6] the following compounds were prepared: *N,N*-Diethyl(*Z*)-2-benzoylamino-3-(2-pyrimidinyl)aminopropenamide (**11a**), *N,N*-diethyl(*Z*)-2-benzoylamino-3-(4-methyl-2-pyrimidinyl)aminopropenamide (**11b**), *N,N*-diethyl(*Z*)-2-benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropenamide (**11c**), *N,N*-diethyl(*Z*)-2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropenamide (**11d**), *N,N*-diethyl(*Z*)-2-benzoylamino-3-(6-chloro-3-pyridazinyl)aminopropenamide (**11f**), and *N,N*-diethyl(*Z*)-2-benzoylamino-3-(2-pyrazinyl)aminopropenamide (**11g**). The experimental and analytical data are summarized in Tables 1 and 2.

(*Z*)-2-Benzoylamino-3-heteroarylaminopropenoylhydrazides **12**.

According to the procedure we have described previously for **12h** [6] the following compounds were prepared: (*Z*)-2-Benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropenoylhydrazide (**12c**), (*Z*)-2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropenoylhydrazide (**12d**), (*Z*)-2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)-aminopropenoylhydrazide (**12e**), and (*Z*)-2-benzoylamino-3-(6-chloro-3-pyridazinyl)aminopropenoylhydrazide (**12f**). The experimental and analytical data are summarized in Tables 1 and 2.

2-Benzoylamino-3-heteroarylamino-5-oxopyrazolidines **13**. General Procedure.

A mixture of **4** (0.001 mole) and hydrazide hydrate (80%, 0.15 ml) in ethanol (5 ml) was heated under reflux for 2 hours. The precipitate was, after cooling to 0°, filtered and the solid was recrystallized from an appropriate solvent. The following compounds were prepared in this manner: 2-Benzoylamino-3-(2-pyrimidinyl)amino-5-oxopyrazolidine (**13a**) and 2-benzoylamino-3-(2-pyrazinyl)amino-5-oxopyrazolidine (**13g**). The experimental and analytical data are summarized in Tables 1 and 2.

(*Z*)-2-Benzoylamino-3-(4-chloro-6-methyl-2-pyridinyl)aminopropenoylazide (**15c**).

This compound was prepared according to the procedure described in lit [6] for **15h**. The experimental and analytical details are given in Tables 1 and 2.

2-Benzoylamino-3-heteroarylaminopropanols **17**. General Procedure.

To a solution of **4** (0.001 mole) in anhydrous ethanol (2.5 ml) sodium borohydride (50 mg) was added and the mixture was heated under reflux for one hour. Water (10 ml) was added to the warm solution and the mixture was left at room temperature overnight. The precipitate was filtered and recrystallized from an appropriate solvent. The following compounds were prepared in this manner: 2-Benzoylamino-3-(2-pyrimidinyl)-aminopropanol (**17a**), 2-benzoylamino-3-(4-methyl-2-pyrimidinyl)amino-propanol (**17b**), 2-benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)-aminopropanol (**17c**), 2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)-aminopropanol (**17d**), 2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)aminopropanol (**17e**), 2-benzoylamino-3-(6-chloro-3-pyridazinyl)aminopropanol (**17f**), and 2-benzoylamino-3-(2-pyrazinyl)amino-propanol (**17g**). The experimental and analytical data are summarized in Tables 1 and 2.

2-Benzoylamino-3-heteroarylaminopropanamides **18**. General Procedure.

To a mixture of **4** (0.001 mole) in ethanol saturated with gaseous ammonia (5 ml) sodium borohydride (50 mg) was added and the mixture was stirred at room temperature for 10 hours. The product was filtered, washed with methanol and ether and recrystallized from an appropriate solvent. The following compounds were prepared in this manner: 2-Benzoylamino-3-(2-pyrimidinyl)aminopropanamide (**18a**), 2-benzoylamino-3-(4-methyl-2-pyrimidinyl)aminopropanamide (**18b**), 2-benzoylamino-3-(4-chloro-6-methyl-2-pyrimidinyl)aminopropanamide (**18c**), 2-benzoylamino-3-(2,6-dimethyl-4-pyrimidinyl)aminopropanamide (**18d**), 2-benzoylamino-3-(5-ethoxycarbonyl-2-methylthio-4-pyrimidinyl)aminopropanamide (**18e**), 2-benzoylamino-3-(6-chloro-3-pyridazinyl)aminopropanamide (**18f**), 2-benzoylamino-3-(2-pyrazinyl)aminopropanamide (**18g**), and 2-benzoylamino-3-(4,6-dimethyl-2-pyrimidinyl)aminopropanamide (**18h**). The experimental and analytical details are given in Tables 1 and 2.

Compound **18h** was prepared from **4h** also by catalytic hydrogenation in the following way:

A mixture of **4h** (0.001 mole) in ethanol (5 ml) and aqueous ammonia (25%, 3 ml) was hydrogenated (3.5 atmospheres) in the presence of Raney nickel (100 mg) at room temperature for 10 hours. The suspension was heated to the boiling, DMF was added in order to dissolve the amide, and the catalyst was collected by filtration. The solid, precipitated from the filtrate after standing at room temperature for several hours, was filtered and recrystallized from a mixture of ethanol and DMF to give **18h** identical with the compound obtained above.

2-Benzoylamino-3-[(*N*-methyl-*N*-heteroaryl)amino]propanamides (**19**). General Procedure.

A mixture of **7** (0.001 mole) and sodium borohydride (50 mg) in ethanol saturated with gaseous ammonia (5 ml) was stirred at room temperature for 12 hours. The suspension was poured into water (20 ml), heated to

boiling and cooled to 0°. The precipitate was filtered and recrystallized from an appropriate solvent. The following compounds were prepared in this manner: 2-Benzoylamino-3-[*N*-methyl-(6-chloro-3-pyridazinyl)amino]-propanamide (**19f**) and 2-benzoylamino-3-[*N*-methyl-*N*-(4,6-dimethyl-2-pyrimidinyl)amino]propanamide (**19h**). The experimental and analytical details are summarized in Tables 1 and 2.

β-Heteroaryiaminoalanines (**20**). General Procedure.

A mixture of **18** (0.001 mole) and hydrochloric acid (20%, 3 ml) was heated under reflux for several hours. Benzoic acid, which precipitates after cooling the reaction mixture to 0°, was collected by filtration. The filtrate was evaporated *in vacuo*, water (2 ml) was added to the residue and the volatile components were evaporated *in vacuo*. The residue was dissolved in water (1 ml), the solution was adjusted to *p*H 7 with aqueous ammonia. The precipitate, formed after standing at room temperature for several hours, was collected by filtration and recrystallized from an appropriate solvent. The following compounds were prepared in this manner:

β-(4-Chloro-6-methyl-2-pyrimidinyl)aminoalanine (**20c**).

This compound was obtained from **18c** in 71% yield, mp 220-225° (from water).

Anal. Calcd. for $C_8H_{11}ClN_4O_2$: C, 41.66; H, 4.81; N, 24.29. Found: C, 41.64; H, 4.87; N, 24.37.

β-(6-Chloro-3-pyridazinyl)aminoalanine (**3f**).

This compound was obtained from **18f** in 95% yield, mp 239-242° (from water).

Anal. Calcd. for $C_7H_9ClN_4O_2$: C, 38.81; H, 4.19; N, 25.86. Found: C, 38.66; H, 4.25; N, 25.67.

β-(4,6-Dimethyl-2-pyrimidinyl)aminoalanine (**20h**).

This compound was prepared from **18h** in 56% yield, mp 245-248° (from water).

Anal. Calcd. for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65. Found: C, 51.13; H, 6.62; N, 26.31.

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