Transformations of 2,2,6-Trimethyl-1,3-dioxen-4-one with Heterocyclic Amines and Other Amino Compounds

Rok Zupet, Miha Tišler* and Ljubo Golič

Department of Chemistry, University of Ljubljana,
61000 Ljubljana, Yugoslavia

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Heterocyclic amines were acetoacetylated with 2,2,6-trimethyl-1,3-dioxen-4-one and the obtained compounds reacted on the reactive methylene group to give *C*-substituted products. Nitrosation, followed by reduction afforded a pyrazine derivative. Azido- or chloroacetamide were also acetoacetylated, with heterocyclic amines, the corresponding enamines were prepared and reduction of the azido group of **15** afforded compounds **22** and/or amides of substituted 3-oxobutanoic acid **23**. An X-ray structural determination of compound **23a** revealed that the orientation about the double bond is *Z*.

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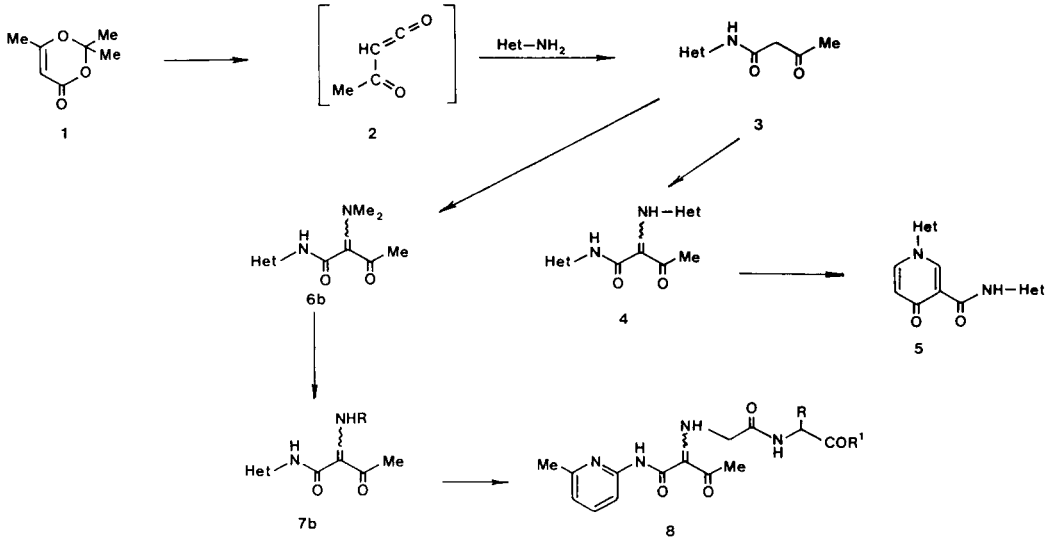
Diketene or ketenes have been used for acetoacetylation of organic compounds [1,2]. Recently, 1,3-dioxin-4-ones were introduced as acylketene equivalents and their applications have been reviewed [3]. So far, some heterocyclic amines were *N*-acetoacetylated with diketene [4] and with excess of the reagent pyridones or 4-pyrones are formed [5]. From 2-aminopyridines pyrido[1,2-*a*]pyrimidin-2- or -4-ones were obtained [6-8]. Similar reactivity has been observed with amides [9-12]. 2,2,6-Trimethyl-1,3-dioxen-4-one (TDO) (**1**) [13] undergoes either thermally or photochemically a retro-Diels-Alder reaction to give acetone and a very reactive acetylketene (**2**) [14]. This makes TDO advantageous to acetoacetic esters or diketene as an acetoacetylation reagent [15,16].

In view of our interest in heterocyclic and other amino acids and their use for syntheses of heterocyclic systems [17-23], it seemed reasonable to examine the possibilities of transformations of heterocyclic amines with TDO. Since it is thermally converted into a reactive acetylketene **2**, reactions with heterocyclic amines have to be run in high boiling solvents. For these purposes xylene or diglyme or excess of TDO could be used. It was found, however, that with excess of TDO dehydroacetic acid was formed as a by-product. It appeared that use of xylene was preferential and that the reaction time could be enormously shortened if a microwave oven was used. In this manner, we have synthesized a number of 3-oxobutanoic acid *N*-(heteroaryl)-amides **3** (Tables 1 and 2). 2-Amino-3-carbethoxypyridine did not react after 4 hours and only dehydroacetic acid



R
CH_2COOEt
$PhCH(COOEt)$
4′-methylphenyl
4′-carbethoxyphenyl
CH_2COOH

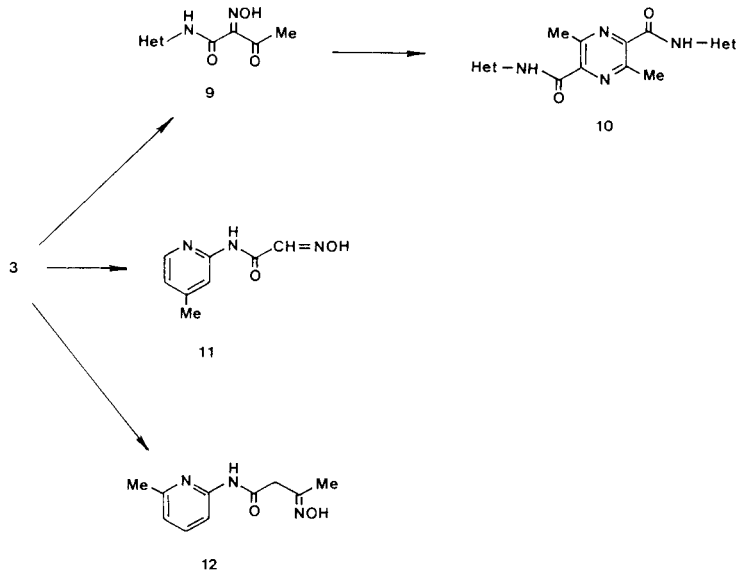
	R	R^1
8-1	CH_2Ph	OEt
8-2	CH_2CHNMe_2	OMe
8-3	CH_2Ph	NH—CHCH$_2$CHMe$_2$ (COOMe)

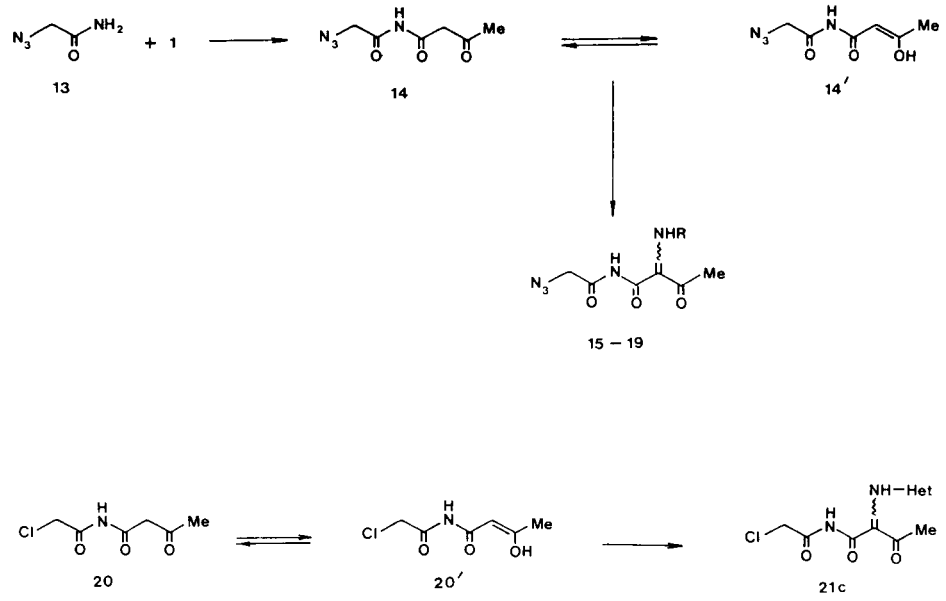
was formed. On hand of ^{1}H nmr spectra these compounds exist exclusively in the keto form. By anticipating a reactive methylene group in **3** we have devised several transformations. One carbon synthon like triethyl orthoformate or *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) reacted unexpectedly in a different manner. The former reagent reacted in boiling toluene with the amides **3** to give the enamines **4** (Tables 3 and 4) instead of the anticipated ethoxymethylene derivatives. For these transformations several reaction paths can be envisaged. One of them may involve the formation of an intermediate ethoxymethyleneamino heterocycle, formed from **3** after desacylation and reacting subsequently with the reactive methylene group of **3**. That this is not the case could be demonstrated by the following experiment. Reaction between **3** and triethyl orthoformate and in the presence of a heterocyclic amine, different from that as incorporated in **3**, afforded only compound **4** with identical heterocyclic residues in the molecule. In another experiment, no reaction could be observed between the ethoxymethyleneamino heterocycle and the reactive methylene group of **3**. From nmr evidence (Table 4) it appears on hand of J_{NHCH} values that the orientation of both hydrogens in the CHNH group is *anti*. The orientation around the double bond is most probably *Z* as in compound **23a** for which an X-ray analysis was made. Compound **4b** reacted with DMF-DMA to give a pyridone derivative **5b** in good yield.

Reaction between **3** and DMF-DMA proceeded as expected to give the enamine and compound **6b** was used as a model for further investigations. The dimethylamino group in **6b** is readily displaced with either esters of amino acids or aromatic amines to give compounds **7**. The enamine part as well as the amide group in **7** (R = CH_2COOEt) are resistant to alkaline hydrolysis and the acid **7** (R = CH_2COOH) was obtained. The acid served for the preparation of some di- and tripeptides **8** using 1,3-dicyclohexylcarbodiimide in the presence of *N*-methylmorpholine [24]. Compounds **8** represent unsaturated and with a heterocyclic residue substituted peptides which are of interest as potential angiotensin converting enzyme (ACE) inhibitors with greater proteolytic stability [25].

Acetoacetylated heterocyclic amines **3** gave upon nitrosation the corresponding hydroxyimino derivatives **9**. It has been previously reported that *N*-alkyl substituted amides of 3-oxobutanoic acid were nitrosated with nitrosyl chloride [26]. As evident from ^{1}H nmr spectra the tautomeric nitroso form is not present. The hydroxyimino group can be reduced, but as shown in the case of compound **9b**, the formed amine is immediately condensed to form the pyrazine derivative **10b**. Compound **3a**, however, did not follow the above reaction pattern and was transformed after nitrosation into **11**. From several runs under identical reaction conditions only this compound was isolated and tlc monitoring showed that in about 2 minutes the reaction was over. Apparently, the acetyl group is cleaved, the transformation being similar to that of ethyl acetoacetate with nitrosyl sulfate in sulfuric acid to give ethyl oximinoacetate [27]. These cases represent a transformation related to the Japp-Klingemann reaction [28]. With hydroxylamine **3b** yielded the anticipated oxime **12b**.

As an extension of the above experiments the behaviour of some amides was investigated. Azidoacetamide (**13**) reacted with TDO to yield the acetoacetylated product **14**. On hand of the ^{1}H nmr spectrum compound **14** exists in solution in deuteriochloroform in equilibrium with its enolic tautomer **14'** in ratio of 2.85:1 at room temperature. This contrasts the above mentioned products **3** where no enolization could be detected. Compound **14** when treated with triethyl orthoformate and in the presence of a hetero-





cyclic amine yielded the corresponding enamines **15** (Tables 5 and 6). With other amino compounds the related derivatives **16-19** were obtained. As in the case of **14**, compound **20** exists in solution in equilibrium with its enol form **20'** and from ^{1}H nmr a ratio of 5:1 could be observed at room temperature. Therefore, both **14** and **20** are soluble in aqueous sodium bicarbonate solution, but they are unsoluble in hot water. Chloroacetamide reacted with **1** to give **20** and further **21c**.

We tried to reduce the azido group of **15** with various reducing agents but none led to the desired amino compound. Sodium cyanoborohydride, sodium borohydride, hydrogen and palladized carbon or ammonium formate in the presence of palladized carbon or even ammonia transformed **15** either in the amide **23** alone or into a mixture with compound **22** (Tables 7 and 8). Reduction with sodium borohydride was very fast and afforded in moderate yield only **23**. Compounds **23** are apparently formed by elimination of the azidoacetyl part in **15** and, interestingly, the double bond remained unchanged. An X-ray analysis of compound **23a** revealed that the orientation at the carbon-carbon double bond is *Z* (Figure 1) [29]. Analyt-

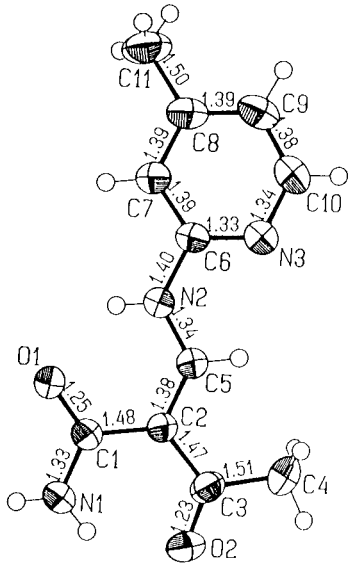


Figure 1. X-Ray structure of compound **23**.

Heterocyclic moieties are:

a, 4'-methylpyridyl-2'-
b, 6'-methylpyridyl-2'-
c, 4',6'-dimethylpyridyl-2'-
d, 3'-carbethoxypyridyl-2'-
e, pyridazinyl-3'-
f, 6'-chloropyridazinyl-3'-
g, pyrimidyl-2'-
h, 4'-methylpyrimidinyl-2'-
i, 4',6'-dimethylpyrimidinyl-2'-
j, pyrazinyl-2'-
k, 3-carboxypyrazinyl-2'-
l, indazolyl-6'-
m, purinyl-6'-

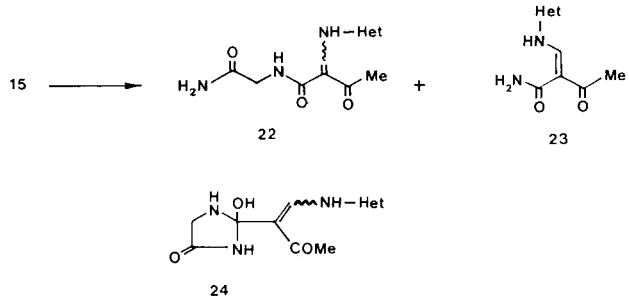


Table 1
3-Oxobutanoic Acid *N*-Heteroarylamides **3**

Compound	Procedure	Yield %	Mp °C	Formula	Analysis Calcd. %C	%H	%N	Found %C	%H	%N
3a	A	95	119-123	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.35	6.31	14.60
3b	A	64	123-125	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.81	6.35	14.69
3f	B	91								
	A	92	206-209	$C_8H_8ClN_3O_2$	44.98	3.77	19.67	45.14	3.88	20.06
3g	A	96	165-166	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.34	5.07	23.64
	B	90								
3j	A	94	130-131 [a]	$C_8H_9N_3O_2$	53.62	5.06	23.45	53.38	5.22	23.45

[a] Crystallized from benzene.

Table 2
^{1}H NMR Data for **3**

Compound	Solvent	δ [ppm]
3a	deuterio-chloroform	2.31 and 2.36 (2s, 6H, two Me), 3.60 (s, 2H, CH_2), 6.88 (d, 1H, $H_{5'}$), 8.01 (s, 1H, $H_{3'}$), 8.15 (d, 1H, $H_{6'}$), 9.2 (s, 1H, NH), $J_{5',6'}$ = 5.08 Hz
3g	deuterio-chloroform	2.33 (s, 3H, COMe), 4.06 (s, 2H, CH_2), 7.02 (t, 1H, $H_{5'}$), 8.62 and 8.67 (2d, 2H, $H_{4'}$ and $H_{6'}$), 10.28 (1s, 1H, NH), $J_{H_{4'},H_{5'}} = J_{H_{5'},H_{6'}} = 4.8$ Hz
3j	DMSO-d_6	2.35 (s, 3H, COMe), 3.65 (s, 2H, CH_2, 8.32 and 8.35 (2d, 2H, $H_{5'}$ and $H_{6'}$), 9.14 (s, 1H, $H_{3'}$), 11.5-11.8 (broad s, 1H, NH), $J_{H_{5'},H_{6'}} = 3.0$ Hz
3b	deuterio-chloroform	2.30 and 2.45 (2s, 6H, 6'-Me and COMe), 3.6 and (s, 2H, CH_2), 6.90 (d, 1H, $H_{5'}$), 7.6 (t, 1H, $H_{4'}$), 7.9 (d, 1H, $H_{3'}$), 9.0-9.3 (broad s, 1H, NH), $J_{H_{3'},H_{4'}} = J_{H_{4'},H_{5'}} = 7.5$ Hz

ical and spectral characteristics for compounds **22** are compatible also with an imidazolidine structure such as **24**. This is, however, excluded on hand of the following observations. Compounds **22** are stable and are thermally not transformed into **23**. They all melt over 200° and when melted they solidify back unchanged. For compounds **24** one could postulate an easy elimination of water, but compounds **22** are stable in ethanolic or aqueous hydrochloric acid. The ^{1}H nmr spectra reveal exchangeable hydrogen atoms of hydroxyl and amino groups. The methylene group appears as a doublet and after addition of deuterium oxide it is transformed into a singlet.

EXPERIMENTAL

Melting points were taken on a Kofler micro stage. All ^{1}H nmr spectra were obtained on a Varian EM 360 L or JEOL JNM FX90Q instrument, using TMS as the internal standard. The ir spectra were recorded on a Perkin-Elmer 1310 spectrometer and mass spectra with a CEC-20-110 C instrument. Elemental analyses (C,H,N) were performed with a Perkin-Elmer 240C Analyzer. The tlc analysis was carried out on Fluka silica gel tlc cards or on DC Fertigplatten Kieselgel 60 F-254, Merck, using a mixture of chloroform and methanol, 10:1, as the solvent, if not otherwise indicated. The molecular structure was determined by single crystal structure X-ray analysis. Enraf-Nonius CAD-4 diffractometer and graphite-monochromated MoKα radiation (λ = 0.71069 Å) were used. Full results of the structure will be published separately.

General Procedure for the Preparation of 3-Oxobutanole Acid *N*-Heteroarylamides **3**.

Procedure A.

A solution of aminoheterocycle (20 mmoles) in dry xylene (50 ml) was treated with TDO **1** (22 mmoles) and the reaction mixture was heated under reflux for 2 hours. Upon cooling the separated product was filtered and crystallized from 1-propanol. The products and their analytical data are presented in Table 1.

Procedure B.

A solution of aminoheterocycle (2 mmoles) in 2-methoxyethyl ether (10 ml) was treated with TDO **1** (2 mmoles). The mixture was heated in a microwave oven 4 times for 20 seconds with cooling intervals. Upon evaporation of the solvent the product was crystallized from 1-propanol. The products are presented in Table 1.

General Procedure for the Preparation of 2-(Heteroaryl)aminomethylene-3-oxobutanoic Acid *N*-(Heteroaryl)amides **4**.

A mixture of the amide **3** (10 mmoles), toluene (50 ml) and triethyl orthoformate (11 moles) was heated under reflux for 1 hour. Upon cooling the separated product was filtered and crystallized either from 1-propanol or toluene. The obtained products and their analytical data are collected in Tables 3 and 4.

1-(6''-Methylpyridyl-2''-)-4-oxopyridine-3-*N*-(6'-methylpyridyl-2'-)-carboxamide (**5b**).

A mixture of compound **4b** (0.31 g, 1 mmole), dry toluene (10 ml) and DMF-DMA (0.3 ml) was heated under reflux for 1 hour,

Table 3

2-(Heteroaryl)aminomethylene-3-oxobutanoic Acid *N*-(Heteroaryl)amides 4

Compound	Yield %	Mp °C	Formula	Analysis					
				Calcd.			Found		
				%C	%H	%N	%C	%H	%N
4a	62	195-196	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	65.72	5.90	18.13
4b	64	185-186	$C_{17}H_{18}N_4O_2$	65.79	5.85	18.05	66.12	6.01	18.02
4c	51	225-227	$C_{19}H_{22}N_4O_2$	67.43	6.55	16.56	67.70	6.89	16.94
4j	90	223-226	$C_{13}H_{12}N_6O_2$	54.92	4.26	29.57	55.29	4.39	29.28

Table 4

^{1}H NMR Data for 4 (in deuteriochloroform)

Compound	δ [ppm]
4c	2.25 (s, 6H, two Me), 2.4 (s, 3H, COMe), 2.45 (2s, 6H, two Me), 6.55 (s, 1H, $H_{3''}$), 6.70 and 6.75 (2s, 2H, $H_{5'}$ and $H_{5''}$), 7.9 (s, 1H, $H_{3'}$), 9.25 (d, 1H, NHC*H*=), 12.0 (d, 1H, N*H*CH=), 12.55 (s, 1H, NH), J_{NHCH} = 12.0 Hz
4j	2.55 (s, 3H, Me), 8.30 (2d, 2H, $H_{5'}$ and $H_{5''}$), 8.40 (s, 1H, $H_{3''}$), 8.50 (2d, 2H, $H_{6'}$ and $H_{6''}$), 9.25 (d, 1H, NHC*H*=), 9.60 (s, 1H, $H_{3'}$), 12.25 (s, 1H, NH), 12.9 (d, 1H, N*H*CH=), J_{NHCH} = 12.0, $J_{H_{5'},H_{6'}} = J_{H_{5''},H_{6''}}$ = 1.0 Hz
4b	2.45 (s, 3H, COMe), 2.50 (s, 6H, two Me), 6.70 (d, 1H, $H_{5''}$), 6.85 (d, 1H, $H_{3''}$), 6.90 (d, 1H, $H_{5'}$), 7.55 (2t, 2H, $H_{4'}$ and $H_{4''}$), 7.95 (d, 1H, $H_{3'}$), 9.25 (d, 1H, NHC*H*=), 12.0 (s, 1H, NH), 12.60 (d, 1H, N*H*CH=), J_{NHCH} = 12.0, $J_{H_{3'},H_{4'}} = J_{H_{4'},H_{5'}}$ = 8.0 Hz
4a	2.34 and 2.37 (2s, 6H, Het-Me), 2.49 (s, 3H, Me), 6.76 (d, 1H, $H_{3''}$), 6.83 and 6.88 (2dd, 2H, $H_{5'}$ and $H_{5''}$), 8.00 (d, 1H, $H_{3'}$), 8.21 (2d, 2H, $H_{6'}$ and $H_{6''}$), 9.23 (d, 1H, NHC*H*=), 12.08 (s, 1H, NH), 12.60 (d, 1H, N*H*CH=), J_{NHCH} = 11.75, $J_{H_{3'},H_{5'}} = J_{H_{3''},H_{5''}}$ = 0.6, $J_{H_{5'},H_{6'}} = J_{H_{5''},H_{6''}}$ = 5.08 Hz

Table 5

Compounds 15

Compound	Reaction time, hours	Yield %	Mp °C	Solvent for crystallization	Formula	Analysis					
						Calcd.			Found		
						%C	%H	%N	%C	%H	%N
15a	0.66	82	188-190 dec	1-propanol	$C_{13}H_{14}N_6O_3$	51.65	4.67	27.80	51.65	4.75	27.72
15b	1.5	76	201-202 dec	ethanol	$C_{13}H_{14}N_6O_3$	51.65	4.67	27.80	52.00	4.76	27.79
15c	1.5	46	210-213 dec	ethanol: 1-propanol, 2:1	$C_{14}H_{16}N_6O_3$	53.16	5.10	26.57	53.08	5.22	26.16
15d	0.3	63	200-203 dec	toluene, then 1-propanol	$C_{15}H_{16}N_6O_5$	50.00	4.48	23.23	50.25	4.61	23.48
15e	2	55	157-161 dec	tolulene, then 1-propanol	$C_{11}H_{11}N_7O_3$	45.67	3.83	33.89	45.75	3.97	34.12
15g	1.5	68	183-187 dec	tolulene, then 1-propanol	$C_{11}H_{11}N_7O_3$	45.67	3.83	33.89	45.48	3.83	34.05
15h	1	53	177-179 dec	1-propanol	$C_{12}H_{13}N_7O_3$	47.52	4.32	32.32	47.23	4.30	32.60
15i	2	52	206-210 dec	ethanol	$C_{13}H_{15}N_7O_3$	49.05	4.75	30.80	49.05	4.65	30.88
15j	2	65	163-164 dec	1-propanol: ethanol, 2:1	$C_{11}H_{11}N_7O_3$	45.67	3.83	33.89	45.75	3.97	34.12
15k	1.5	65	180-183 dec	DMF, then 1-propanol	$C_{12}H_{11}N_7O_5$	43.25	3.33	29.42	43.05	3.51	29.40
15l	1	71	190-192 dec	1-propanol	$C_{14}H_{13}N_7O_3$	51.39	4.00	29.96	51.29	3.94	29.94
15m	1	81	235-237 dec	DMF	$C_{12}H_{11}N_9O_3$	43.77	3.37	38.30	44.02	3.62	38.40

the solvent was evaporated and the residue was crystallized from *n*-heptane (0.23 g, 72% yield), mp 225-227°; ^{1}H nmr (deuteriochloroform): δ 2.50 and 2.65 (2s, 6H, 2Me), 6.70 (d, 1H, $H_{5''}$), 6.90 (2d, 2H, $H_{3''}$ and $H_{5'}$), 7.25 (t, 1H, $H_{4''}$), 7.30 (d, 1H, H_5), 7.70 (t, 1H, $H_{4'}$), 8.15 (d, 1H, $H_{3'}$), 8.40 (dd, 1H, H_6), 8.35 (d, 1H, H_2), 12.65 (s, 1H, NH); J_{H_5,H_6} = 8.0, J_{H_2,H_6} = 1.5, $J_{H_{3'},H_{4'}} = J_{H_{3''},H_{4''}}$ = 8.0 Hz.

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.86; H, 5.21; N, 17.34.

2-(*N*,*N*-Dimethylaminomethylene)-3-oxobutanoic Acid *N*-(6′-Methylpyridyl-2′)amide (**6b**).

A mixture of the amide **3b** (1.92 g, 10 mmoles), methylene chloride (20 ml) and DMF-DMA (1.5 ml) was stirred at room tempera-

ture for 1 hour and then heated under reflux for 20 minutes. The solvent was evaporated and the oily residue crystallized gradually. The product was crystallized from benzene (1.78 g, 72% yield), mp 128-132°; ^{1}H nmr (deuteriochloroform): δ 2.25 and 2.45 (2s, 6H, COMe and 6'-Me), 3.15 (s, 6H, NMe_2), 7.85 (d, 1H, $H_{5'}$), 7.55 (t, 1H, $H_{4'}$), 7.70 (s, 1H, CH=), 8.15 (d, 1H, $H_{3'}$), 10.2 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.62; H, 6.32; N, 16.08.

Reaction of the Enamine **6b** with Esters of Amino Acids and Aromatic Amines to Give Compounds **7**.

To a solution of the enamine **6b** (2.47 g, 10 mmoles) in ethanol (10 ml) glycine ethyl ester hydrochloride (1.39 g, 10 mmoles) was added and the mixture was heated under reflux for 1 hour. The solvent was evaporated and the solid residue of **7** (R = CH_2COOEt) was crystallized from 1-propanol (2.56 g, 84% yield), mp 100-102°; ^{1}H nmr (deuteriochloroform): δ 1.3 (t, 3H, CH_2CH_3), 2.3 and 2.5 (2s, 6H, Het-Me and COMe), 4.2 (d, 2H, CH_2COOEt), 4.35 (q, 2H, CH_2Me), 6.9 (d, 1H, $H_{5'}$), 7.6 (t, 1H, $H_{4'}$), 7.9 (d, 1H, NHCH=), 8.1 (d, 1H, $H_{3'}$), 11.6-12.3 (broad, 1H, NHCH=), 12.15 (s, 1H, NH); J_{NHCH} = 13.0, $J_{H_{3'},H_{4'}}$ = 6.0, J_{Et} = 7.0 Hz.

Anal. Calcd. for $C_{15}H_{19}N_3O_4$: C, 59.00; H, 6.27; N, 13.67. Found: C, 59.13; H, 6.50; N, 13.67.

In essentially the same manner the following compounds were prepared:

Compound **7** (R = CH(Ph)COOEt was prepared from L-phenylalanine ethyl ester hydrochloride in 89% yield, mp 139-141° (from propyl ether).

Anal. Calcd. for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.63. Found: C, 66.85; H, 6.35; N, 10.67.

Compound **7** (R = *p*-tolyl) was prepared from *p*-toluidine in 94% yield, mp 155-157° (from 1-propanol).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.15; H, 6.26; N, 13.71.

Compound **7** (R = *p*-carbethoxyphenyl) was prepared from ethyl *p*-aminobenzoate in 92% yield, mp 204-205° (from ethanol).

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.67; N, 11.44. Found: C, 65.32; H, 5.81; N, 11.46.

The ester **7** (R = CH_2COOEt) was hydrolyzed with aqueous potassium hydroxide (10 *M*) at room temperature to give the corresponding acid **7** (R = CH_2COOH) in 68% yield, mp 124-126° (from ethanol).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.16. Found: C, 56.52; H, 5.60; N, 15.00.

General Procedure for the Formation of the Peptide Bond Using the DCC Method. Preparation of Compounds **8**.

To a solution of the acid **7** (R = CH_2COOH) (0.554 g, 2 mmoles) and the ester of amino acid or dipeptide (2 mmoles) in dry methylene chloride (5 ml) *N*-methylmorpholine (0.202 g, 2 mmoles) was added and the reaction mixture was cooled to 0-5°. To the solution 1,3-dicyclohexylcarbodiimide (0.412 g, 2 mmoles) was added, the reaction mixture was stirred for 1 hour and the separated urea derivative was filtered. The filtrate was washed with two portions of 1 ml of water, dried, filtered and the solvent was evaporated *in vacuo*. The residue was crystallized from 1-propanol. In this manner the following compounds were prepared:

Compound **8-1** was prepared from L-phenylalanine ethyl ester in 90% yield, mp 194-196°; ^{1}H nmr (DMSO-d_6): δ 1.15 (t, 3H, CH_2CH_3), 2.35 and 2.45 (2s, 6H, two Me), 3.05 (d, 2H, CH_2Ph), 4.2 (q, 2H, CH_2Me), 4.25 (d, 2H, $NHCH_2$), 4.55 (q, 1H, CH_2CH), 6.95 (d, 1H, $H_{5'}$), 7.25 (s, 5H, Ph), 7.65 (t, 1H, $H_{4'}$), 8.05 (d, 1H, $H_{3'}$), 8.20 (d, 1H, NHCH=), 8.70 (d, 1H, CONHCH), 10.5 (broad, 1H, NHCH=), 12.50 (s, 1H, NH), J_{Et} = 7.0, J_{NHCH} = 15.0, J_{CONHCH} = 8.0, J_{NHCH_2} = 8.0, J_{CHCH_2} = 8.0, $J_{H_{3'},H_{4'}}$ = $J_{H_{4'},H_{5'}}$ = 7.0 Hz.

Anal. Calcd. for $C_{24}H_{28}N_4O_5$: C, 63.70; H, 6.24; N, 11.38. Found: C, 63.34; H, 6.45; N, 11.82.

Compound **8-2** was prepared from L-leucine methyl ester in 75% yield, mp 140-143°; ^{1}H nmr (DMSO-d_6): δ 0.85 and 0.92 (two d, 6H, $CH(CH_3)_2$), 1.3-1.8 (m, 3H, $CHMe_2$ and CH_2CHMe_2), 2.28 and 2.38 (2s, 6H, COMe and Het-Me), 3.65 (s, 3H, COOMe), 4.21 (d, 2H, $COCH_2NH$), 4.18-4.35 (m, 1H, NHCHCOOMe), 6.90 (d, 1H, $H_{5'}$), 7.61 (t, 1H, $H_{4'}$), 7.97 (d, 1H, $H_{3'}$), 8.20 (d, 1H, NHCH=), 8.58 (d, 1H, CONHCH), 10.53 (m, 1H, NHCH=), 12.14 (s, 1H, NH), J_{NHCH} = 13.65, J_{CONHCH} = 7.60, $J_{H_{3'},H_{4'}}$ = $J_{H_{4'},H_{5'}}$ = 7.0, J_{NHCH_2} = 5.70, J_{CHMe} = 3.50 Hz.

Anal. Calcd. for $C_{20}H_{28}N_4O_5$: C, 59.39; H, 6.98; N, 13.85. Found: C, 59.23; H, 7.12; N, 13.70.

Compound **8-3** was prepared from L-phenylalanyl-L-leucine methyl ester in 56% yield, mp 212-214°; ^{1}H nmr (DMSO-d_6): δ 0.85 (d, 6H, $CH(CH_3)_2$), 1.2-1.6 (m, 3H, CH_2CHMe_2, $CHMe_2$), 2.3 and 2.4 (2s, 6H, Het-Me and COMe), 3.1 (d, 2H, CH_2Ph), 3.55 (s, 3H, COOMe), 2.4 (d, 2H, $COCH_2NH$), 4.1-4.6 (m, 2H, 2NHCHCO), 6.9 (d, 1H, $H_{5'}$), 7.3 (s, 5H, Ph), 7.7 (t, 1H, $H_{4'}$), 8.05 (d, 1H, $H_{3'}$), 8.2 (d, 1H, NHCH=), 8.3 and 8.55 (2d, 2H, NHCHCO), 10.4-10.9 (broad, 1H, NHCH=), 12.3 (s, 1H, NH), J_{NHCH} = 14.0, J_{CHMe} = 3.0, $J_{H_{3'},H_{4'}}$ = $J_{H_{4'},H_{5'}}$ = 7.0, J_{NHCH_2} = 7.0, J_{CHCH_2Ph} = J_{NHCHR} = 8.0 Hz.

Anal. Calcd. for $C_{29}H_{37}N_5O_6$: C, 63.14; H, 6.76; N, 12.70. Found: C, 62.98; H, 7.00; N, 12.62.

Reaction of *N*-(Heteroaryl)amides of 3-Oxobutanoic Acid (**3**) with Nitrous Acid.

The amide **3** (5 mmoles) was dissolved in glacial acetic acid (10 ml) and under stirring sodium nitrite (0.38 g, 5.5 mmoles) was added portionwise. The reaction mixture was stirred at 10° for 30 minutes, cold (5°) water (20 ml) was added and the separated product was filtered. In this manner the following compounds were prepared:

Compound **9g** was obtained in 65% yield, mp 179-181° (from 1-propanol); ^{1}H nmr (deuteriochloroform): δ 2.30 (s, 3H, Me), 7.15 (t, 1H, $H_{5'}$), 8.57 (d, 2H, $H_{4'}$ and $H_{6'}$), 11.23 and 12.31 (2s, 2H, NH, NOH), $J_{H_{4'},H_{5'}}$ = 5.08 Hz.

Anal. Calcd. for $C_8H_8N_4O_3$: C, 46.15; H, 3.87; N, 26.92. Found: C, 46.28; H, 3.91; N, 26.85.

Compound **9b** was obtained in 60% yield, mp 168-172° (from ethyl acetate); ^{1}H nmr (DMSO-d_6): δ 2.30 and 2.35 (two s, 6H, two Me), 7.1 (d, 1H, $H_{5'}$), 7.75 (t, 1H, $H_{4'}$), 8.00 (d, 1H, $H_{3'}$), 10.8 (s, 1H, NH), 12.1-12.6 (broad, 1H, NOH), $J_{H_{3'},H_{4'}}$ = 6.0 Hz.

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.22; H, 5.11; N, 18.91.

Compound **11** was obtained in 45% yield, mp 206-208° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 2.36 (s, 3H, Me), 7.06 (d, 1H, $H_{5'}$), 7.91 (s, 1H, $H_{3'}$), 8.13 and 8.41 (broad, 2H, CH=NOH), 8.23 (d, 1H, $H_{6'}$), 9.85 (s, 1H, NH), $J_{H_{5'},H_{6'}}$ = 4.5 Hz; ms: (m/e, %) 179 (M^+, 8%), 135 (100%).

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.62; H, 5.06; N, 23.45. Found: C, 53.75; H, 5.11; N, 23.31.

3,6-Dimethylpyrazine-2,5-dicarboxylic Acid Bis-(6'-methylpyridyl-2')amide (**10b**).

To a solution of compound **9b** (1.1 g, 5 mmoles) in ethanol (20 ml), ethanolic hydrogen chloride (1 ml of 3%) and palladized carbon (0.1 g of 5%) were added. The mixture was stirred in an atmosphere of hydrogen for 2 hours, filtered and the solvent evaporated. From the cold residue the solid material was separated, dissolved in water (5 ml) and neutralized with solid sodium bicarbonate. The separated product was filtered and crystallized from benzene (0.4 g, 43% yield), mp >260°; ^{1}H nmr (deuteriochloroform): δ 2.5 (two s, 6H, two Me), 3.1 (s, 6H, two Me), 7.05 (d, 2H, two $H_{5'}$), 7.7 (t, 2H, two $H_{4'}$), 8.25 (d, 2H, two $H_{3'}$), 10.5 (s, 2H, two NH), $J_{H_{3'},H_{4'}}$ = 6.0 Hz.

Anal. Calcd. for $C_{20}H_{20}N_6O_2$: C, 63.82; H, 5.36; N, 22.33. Found: C, 63.59; H, 5.68; N, 22.48.

3-Hydroxyiminobutanoic Acid *N*-(6'-Methylpyridyl-2')amide (**12**).

To a solution of the amide **3b** (0.576 g, 3 mmoles) in ethanol (25 ml) finely powdered hydroxylamine hydrochloride (0.208 g, 3 mmoles) was added and the mixture was stirred at room temperature for 20 minutes. Thereafter triethylamine (0.303 g, 3 mmoles) was added and the reaction mixture was heated under reflux for 10 minutes. Upon cooling the separated product was filtered and crystallized from ethanol (1.0 g, 96%), mp 135-138°; ^{1}H nmr (deuteriochloroform): δ 2.20 and 2.46 (2s, 6H, two Me), 3.42 (s, 2H, CH_2), 6.91 (d, 1H, $H_{5'}$), 7.66 (t, 1H, $H_{4'}$), 8.15 (d, 1H, $H_{3'}$), 10.26 (s, 1H, NH), 10.93 (broad s, 1H, OH), $J_{H_{3'},H_{4'}}$ = 6.0 Hz; hrms: (m/e) 207.1000 (M^+, 20%), 135 (100%); Calcd: M^+ = 200.1008.

3-Oxobutanoic Acid Azidoacetamide (**14**).

A mixture of azidoacetamide (**13**) (13.1 g, 0.131 mmole), TDO (**1**) (20.5 g, 0.145 mmole) and dry xylene (40 ml) was heated under reflux for 3 hours. Upon cooling the separated product was filtered and crystallized from benzene and thereafter from propyl ether to give 15.5 g (76% yield) of compound **14**, mp 106-110°; ir: 2150 (N_3), 1760 and 1720 cm^{-1} (CO); ^{1}H nmr (deuteriochloroform): two forms **14** and **14'** in ratio of 2.85:1; Form **14**: δ 2.3 (s, 3H, Me), 3.85 (s, 2H, CH_2N_3), 4.2 (s, 2H, CH_2COMe), 13.3 (s, 1H, NH); Form **14'**: δ 2.1 (s, 3H, Me), 4.25 (s, 2H, CH_2N_3), 5.9 (s, 1H, -CH=), 8.6-8.9 and 9.2-9.7 (broad s, 2H, NH and OH).

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.13; H, 4.38; N, 30.43. Found: C, 39.06; H, 4.36; N, 30.46.

General Procedure for the Conversion of 3-Oxobutanoic Acid Azidoacetamide with Triethyl Orthoformate and Heterocyclic Amines.

The azide **14** (3 mmoles), triethyl orthoformate (3.3 mmoles), the corresponding aminoheterocycle (3 mmoles) and toluene (2 ml) were heated under reflux as indicated in Table 5. Progress of the reaction was followed by tlc. Upon cooling the reaction mix-

Table 6
^{1}H NMR Data for 15

Compound	Solvent	δ [ppm]
15i	deuteriochloroform	2.46 (s, 6H, 4'- and 6'-Me), 2.50 (s, 3H, COMe), 4.39 (s, 2H, N_3CH_2 -), 6.84 (s, 1H, $H_{5'}$), 9.24 (d, 1H, NHC*H*=), 12.00 (d, 1H, N*H*CH=), 12.3 (s, 1H, NH), J_{NHCH} = 12.7 Hz
15a	deuteriochloroform	2.4-2.5 (two s, 6H, 4'-Me, COMe), 4.35 (s, 2H, CH_2), 6.85 (s, 1H, $H_{3'}$), 7.05 (d, 1H, H_5), 8.3 (d, 1H, $H_{6'}$), 9.35 (d, 1H NHC*H*=), 12.3 (d, 1H, N*H*CH=), 12.7 (s, 1H, NH), $J_{H_{5'},H_{6'}}$ = 5.0, J_{NHCH} = 12.0 Hz
15g	deuteriochloroform	2.5 (s, 3H, Me), 4.4 (s, 2H, CH_2), 7.15 (t, 1H, $H_{5'}$), 8.65 (d, 2H, $H_{4'}$ and $H_{6'}$), 9.25 (d, 1H, NHC*H*=), 12.15 (d, 1H, N*H*CH=), 12.40 (s, 1H, NH), $J_{H_{4'}}$ and $H_{5'}$ = 4.8, J_{NHCH} = 12.0 Hz
15c	deuteriochloroform	2.33 (s, 3H, Me), 2.5 (two s, 6H, 4'- and 6'-Me), 4.31 (s, 2H, CH_2), 6.59 and 6.84 (2s, 2H, $H_{3'}$ and $H_{5'}$), 9.33 (d, 1H, NHC*H*=), 12.15 (d, 1H, N*H*CH=), 12.6 (s, 1H, NH), J_{NHCH} = 12.5 Hz
15e	DMSO-d_6	2.50 (s, 3H, Me), 4.5 (s, 2H, CH_2), 7.75 (dd, 1H, $H_{5'}$), 8.02 (dd, 1H, $H_{4'}$), 9.09 (dd, 1H, H6'), 9.25 (d, 1H, NHC*H*=), 12.01 (d, 1H, N*H*CH=), 12.2 (s, 1H, NH), J_{NHCH} = 12.0, $J_{H_{4'},H_{5'}}$ = 8.9, $J_{H_{4'},H_{6'}}$ = 1.3 Hz
15j	DMSO-d_6	2.50 (s, 3H, Me), 4.35 (s, 2H, CH_2), 8.3-8.6 (m, 3H, $H_{3'}$, $H_{5'}$, $H_{6'}$), 9.25 (d, 1H, NHC*H*=), 12.2-12.8 (broad s, 2H, two NH), J_{NHCH} = 12.0 Hz
15b	DMSO-d_6	2.45 and 2.53 (2s, 6'-Me and COMe), 4.43 (s, 2H, CH_2), 7.07 (d, 1H, $H_{5'}$), 7.20 (d, 1H, $H_{3'}$), 7.71 (t, 1H, $H_{4'}$), 9.18 (d, 1H, NHC*H*=), 11.85 (d, 1H, N*H*CH=), 12.18 (s, 1H, NH), J_{NHCN} = 14.0, $J_{H_{3'},H_{4'}}$ = $J_{H_{4'},H_{5'}}$ = 7.6 Hz
15h	deuteriochloroform	3.5 (s, 6H, 4'-Me and COMe), 4.4 (s, 2H, CH_2), 7.05 (d, 1H, $H_{5'}$), 8.55 (d, 1H, $H_{6'}$), 9.3 (d, 1H, NHC*H*=), 12.1 (d, 1H, N*H*CH=), 12.4 (s, 1H, NH), J_{NHCH} = 13.0, $J_{H_{5'},H_{6'}}$ = 6.0 Hz
15d	deuteriochloroform	1.55 (t, 3H, CH_2CH_3), 2.6 (s, 3H, COMe), 4.6 (s, 2H, CH_2N_3), 4.65 (q, 2H, CH_2Me), 7.2-7.5 (m, 1H, $H_{4'}$), 8.4-8.8 (m, 2H, $H_{5'}$ and $H_{6'}$), 9.65 (d, 1H, NHC*H*=), 12.43 (s, 1H, NH), 13.83 (broad d, 1H, N*H*CH=), J_{NHCH} = 12.0 Hz
15l	DMSO-d_6	2.35 (s, 3H, Me), 4.55 (s, 2H, CH_2), 7.35 (dd, 1H, $H_{5'}$), 7.8 (d, 1H, $H_{7'}$), 7.9 (d, 1H, $H_{4'}$), 8.2 (s, 1H, $H_{3'}$), 8.8 (d, 1H, NHC*H*=), 12.25 (d, 1H, N*H*CH=), 12.55 and 13.25 (1s, 2H, two NH), J_{NHCH} = 13.0, $J_{4',5'}$ = 8.0, $J_{5',7'}$ = 1.0 Hz
15m	DMF-d_7	2.5 (s, 3H, Me), 4.55 (s, 2H, CH_2), 7.0-7.2 (broad s, 1H, $H_{9'}$), 8.68 and 8.80 (2s, 2H, $H_{3'}$ and $H_{8'}$), 9.7 (d, 1H, NHC*H*=), 12.2 (s, 1H, NH), 12.45 (d, 1H, N*H*CH=), J_{NHCH} = 12.0 Hz
15k	DMSO-d_6	2.5 (s, 3H, Me), 4.4 (s, 2H, CH_2), 8.65 and 8.80 (2d, 2H, $H_{5'}$ and $H_{6'}$), 9.35 (d, 1H, NHC*H*=), 12.15 (s, 1H, NH), 13.65 (d, 1H, N*H*CH=), J_{NHCH} = 12.0, $J_{H_{5'},H_{6'}}$ = 1.0 Hz

ture the product was filtered and crystallized. The compounds obtained with their analytical data are presented in Table 5. All compounds reveal in their ir spectra the presence of an azido group (2150 cm^{-1}). The ^1H nmr data are given in Table 6.

2-Aminomethylene-3-oxobutanoic Acid *N*-Azidoacetamide (**16**).

A solution of compound **14** (1.84 g, 10 mmoles) in methylene chloride (20 ml) was treated with DMF-DMA (1.5 ml) and the reaction mixture was stirred at room temperature for 20 minutes. The solution was shaken with water (2.5 ml) and the methylene chloride layer separated and dried. Upon evaporation of the solvent the oily residue dissolved in ethanol (20 ml), ammonium chloride (0.588 g, 1.1 mmoles) was added and the reaction mixture was heated slowly until the salt completely dissolved. Upon cooling the separated product was filtered and crystallized three times from ethanol (yield 1.95 g, 94%), mp 203-206° dec; ^1H nmr (DMSO-d_6): δ 2.27 (s, 3H, Me), 4.44 (s, 2H, CH_2), 8.10 and 8.23 (2d, 1H, NHC*H*=), 8.95-9.25 and 9.4-9.9 (2 broad d, 2H, N*H*$_2$CH=), 12.43 (s, 1H, NH), J_{NHCH} and J_{NH_2CH} = 15.53 and 15.62 Hz; ms: (m/e): 211 (M^+, <1%), 183 (M^+ -28, 2%), 155 (100%).

Anal. Calcd. for $C_7H_9N_5O_3$: C, 39.81; H, 4.30; N, 33.17. Found: C, 39.84; H, 4.33; N, 33.20.

Reaction Between 3-Oxobutanoic Acid Azidoacetamide, Triethylorthoformate and Urea to Give **17**.

In essentially the same manner as above, but using a mixture of toluene (5 ml) and 1-propanol (1 ml) from 368 mg of compound **14** after 1.5 hours under reflux the substituted urea derivative **17** was obtained in 92% yield, mp 225° dec (from 1-propanol); ^1H nmr (DMSO-d_6): δ 2.40 (s, 3H, Me), 4.46 (s, 2H, CH_2), 7.43-7.65 and 7.70-8.05 (two broad s, 2H, NH_2), 8.65 (d, 1H, NHC*H*=), 11.31 (d, 1H, N*H*CH=), 12.10 (s, 1H, NH), J_{NHCH} = 13.7 Hz.

Anal. Calcd. for $C_8H_{10}N_6O_4$: C, 37.80; H, 3.97; N, 33.06. Found: C, 38.00; H, 4.12; N, 33.01.

2-Carbethoxymethylaminomethylene-3-oxobutanoic Acid *N*-Azidoacetamide (**18**).

A mixture of compound **14** (0.92 g, 5 mmoles), methylene chloride (10 ml) and DMF-DMA (0.75 ml) was left to stand at room temperature for 20 minutes. The solvent was evaporated at room temperature, ethanol (20 ml) and ethyl glycinate hydrochloride (0.7 g, 5 mmoles) were added. The mixture was heated under reflux for 0.5 hour, the solvent was evaporated and the residual oil gradually solidified. The product was crystallized from 1-propanol (yield 1.1 g, 74%), mp 107-112°; ^1H nmr (deuteriochloroform): δ 1.32 (t, 3H, CH_2CH_3), 2.31 (s, 3H, COMe), 4.28 (d, 2H, NHC*H*$_2$), 4.29 (q, 2H, C*H*$_2$CH$_3$), 4.30 (s, 2H, CH_2N_3), 7.88 (d, 2H, NHC*H*=), 10.5-10.8 (broad d, 1H, N*H*CH=), J_{NHCH} = 13.68, J_{NHCH_2} = 6.5, J_{Et} = 7.08 Hz.

Anal. Calcd. for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 43.97; H, 5.33; N, 23.42.

In a similar manner from glycinamide hydrochloride the amide **19** could be prepared in 87% yield, mp 187-188° dec (from a mixture of ethanol and 1-propanol); ^1H nmr (DMSO-d_6): δ 2.3 (s, 3H, Me), 4.2 (d, 2H, NHC*H*$_2$), 4.45 (s, 2H, N_3CH_2), 7.2 and 7.6 (2s, 2H, $CONH_2$), 8.25 (d, 1H, NHC*H*=), 10.0-10.6 (broad s, 2H, N*H*CH= and NH), J_{NHCH} = 13.6 Hz.

Anal. Calcd. for $C_9H_{12}N_6O_4$: C, 40.30; H, 4.51; N, 31.33. Found: C, 40.47; H, 4.69; N, 31.02.

3-Oxobutanoic Acid Chloroacetamide (**20**).

Table 7

Compounds 22 and 23

Compound	Method	Yield %	Mp °C	Formula	Analysis					
					Calcd.			Found		
					%C	%H	%N	%C	%H	%N
22a	E	16	228-235 [a]	$C_{13}H_{16}N_4O_3$	56.51	5.84	19.83	56.81	6.12	20.28
	F	14								
23a	E	39	186-188	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.15	60.30	6.15	18.77
	F	47								
23c	B	43	178-180	$C_{12}H_{15}N_3O_2$	61.78	6.48	18.02	61.62	6.55	17.93
	C	45								
22d	E	32	222-226 [a]	$C_{15}H_{18}N_4O_5$	53.88	5.43	16.67	53.70	5.90	16.40
23d	A	25	156-162	$C_{13}H_{15}N_3O_4$	56.31	5.45	15.16	56.10	5.68	15.00
	E	51	subl							
22e	E	56	240-243 [a]	$C_{11}H_{13}N_5O_3$	50.18	4.98	26.61	50.19	5.00	26.54
22g	E	30	263-267 [a]	$C_{11}H_{13}N_5O_3$	50.18	4.98	26.61	49.91	4.21	26.17
23g	A	19	203-205	$C_9H_{10}N_4O_2$	52.42	4.89	27.17	51.99	4.95	27.02
	E	51								
	F	65								
22h	E	20	255-257 [a]	$C_{12}H_{15}N_5O_3$	51.98	5.45	25.26	51.95	5.65	25.36
23h	E	45	206-209	$C_{12}H_{12}N_4O_2$	54.54	5.49	25.44	54.36	5.54	25.47
	F	57								
22i	F	44	256-257 [a]	$C_{13}H_{17}N_5O_3$	53.60	5.88	24.04	53.42	6.00	23.97
23j	E	45	179-181	$C_9H_{10}N_4O_2$	51.42	4.89	27.17	51.99	4.95	27.02

[a] From 1-propanol.

The compound was prepared from chloroacetamide (9.35 g, 0.1 mmole) in the same manner as above for **14** after 2 hours under reflux. The compound was crystallized from toluene and propyl ether (15.0 g, 85% yield), mp 142-143°; ^{1}H nmr (DMSO-d_6): two forms in ratio of 5:1; Form **20**: δ 2.2 (s, 3H, Me), 3.8 (s, 2H, CH_2COMe), 4.45 (s, 2H, CH_2Cl), 11.1 (s, 1H, NH); Form **20'**: δ 2.05 (s, 3H, Me), 4.55 (s, 2H, CH_2Cl), 5.7 (s, 1H, -CH=), 10.8-11.3 (broad s, 2H, NH and OH).

Anal. Calcd. for $C_6H_8ClNO_3$: C, 40.58; H, 4.54; N, 7.88. Found: C, 40.52; H, 4.55; N, 7,82.

By the above general procedure from 3-oxobutanoic acid *N*-chloroacetamide and 2-amino-4,6-dimethylpyridine compound **21c** was prepared in 78% yield, mp 220-222° dec (from 1-propanol); ^{1}H nmr (DMF-d_7, 146°): δ 2.34 (s, 3H, Me), 2.46 (s, 6H, 4'-and 6'-Me), 4.66 (s, 2H, CH_2), 6.95 and 7.11 (2s, 2H, $H_{3'}$ and $H_{5'}$), 9.35 (d, 1H, NHC*H*=), 12.15 (broad d, 1H, N*H*CH=), 12.28 (s, 1H, NH), J_{NHCH} = 12.0 Hz.

Anal. Calcd. for $C_{14}H_{15}ClN_3O_3$: C, 54.28; H, 5.20; N, 13.56. Found: C, 54.20; H, 5.33; N, 13.71.

Reduction or Ammonolysis of Azidoacetamides **15**.

Method A.

A solution of the corresponding azidoacetamide **(15)** (1 mmole) in methanol (10 ml) was treated with 1.2 equivalents of sodium cyanoborohydride under stirring. After 2 hours the solvent was evaporated and water (1 ml) was added. The separated product was filtered and crystallized from propyl ether.

Method B.

To an aqueous solution of potassium hydroxide (2 mmoles in 8 ml) the corresponding azidoacetamide **(15)** (1 mmole) was added and under stirring 1.5 equivalents of sodium borohydride was added portionwise. After 30 minutes the reaction mixture was acidified with glacial acetic acid and the separated product was filtered and crystallized from propyl ether.

Method C.

A solution of the corresponding azidoacetamide **(15)** (1 mmole) in methanol (5 ml) was treated with sodium cyanoborohydride (1.2 equivalents) and the reaction mixture was heated under reflux for 30 minutes. After evaporation of the solvent ethanol (1 ml) was added and the separated product was filtered and crystallized from propyl ether.

Table 8

^{1}H NMR Data for 22 and 23

Compound	Solvent	δ [ppm]
23a	deuteriochloroform	2.33 and 2.44 (2s, 6H, 2 Me), 6.72 (d, 1H, $H_{3'}$), 6.87 (dd, 1H, $H_{5'}$), 8.18 (d, 1H, $H_{6'}$), 9.16 (d, 1H, NHC*H*=), 12.7 (d, 1H, N*H*CH=), J_{NHCH} = 11.0, $J_{H3',H5'}$<1, $J_{H5',H6'}$ = 5.1 Hz
23c	deuteriochloroform	2.3 (s, 3H, COMe), 2.45 (s, 6H, 2 Het-Me), 9.25 (d, 1H, NHC*H*=), 12.65 (d, 1H, N*H*CH=), J_{NHCH} = 11.0 Hz
23d	deuteriochloroform	1.42 (t, 3H, CH_2CH_3), 2.49 (s, 3H, COMe), 4.49 (q, 2H, CH_2Me), 7.09 (dd, 1H, $H_{5'}$), 8.37 (dd, 1H, $H_{4'}$), 8.49 (dd, 1H, $H_{6'}$), 9.40 (d, 1H, NHC*H*=), 12.5 (d, 1H, N*H*CH=), J_{NHCH} = 11.5, $J_{H4',H5'}$ = 7.8, $J_{H5',H6'}$ = 4.6, $J_{H4',H6'}$ = 2.7, J_{Et} = 7.08 Hz
23g	DMSO-d_6	2.4 (s, 3H, Me), 7.3 (t, 1H, $H_{5'}$), 8.75 (d, 2H, $H_{4'}$ and $H_{6'}$), 9.1 (d, 1H, NHC*H*=), 12.9 (d, 1H, N*H*CH=), J_{NHCH} = 11.5, $J_{H5',H6'}$ = $J_{H4',H5'}$ = 5.0 Hz
23j	deuteriochloroform	2.46 (s, 3H, Me), 8.30 (d, 1H, $H_{5'}$), 8.32 (s, 1H, $H_{3'}$), 8.37 (d, 1H, $H_{6'}$), 9.08 (d, 1H, NHC*H*=), 11.8 (d, 1H, N*H*CH=), J_{NHCH} = 11.5, $J_{H5',H6'}$ = 1.3 Hz
23h	deuteriochloroform	2.45 and 2.49 (2s, 6H, 2 Me), 6.88 (d, 1H, $H_{5'}$), 8.39 (d, 1H, $H_{6'}$), 9.10 (d, 1H, NHC*H*=), 12.48 (d, 1H, N*H*CH=), J_{NHCH} = 12.06, $J_{H5',H6'}$ = 5.07 Hz
22g	DMSO-d_6	2.42 (s, 3H, Me), 3.9 (d, 2H, NHCH_2,), 7.0-7.3 and 7.4-7.7 (broad, 2H, OH and NH), 7.35 (t, 1H, $H_{5'}$), 7.8 (d, 2H, $H_{4'}$ and H_6), 9.05 (d, 1H, NHC*H*=), 9.75 (t, 1H, N*H*CH_2), 12.7 (d, 1H, N*H*CH=), J_{NHCH} = 11.5, J_{NHCH_2} = 5.0, $J_{H4',H5'}$ = $J_{H5',H6'}$ = 4.0 Hz
22h	DMSO-d_6	2.4 (s, 3H, COMe), 2.45 (s, 3H, Het-Me), 3.9 (d, 2H, NHCH_2,), 7.0-7.3 and 7.35-7.6 (broad, 2H, NH and OH), 7.2 (d, 1H, $H_{5'}$), 7.6 (d, 1H, $H_{4'}$), 9.15 (d, 1H, NHC*H*=), 9.8 (t, 1H, N*H*CH_2), 12.7 (d, 1H, N*H*CH=), J_{NHCH} = 12.0, J_{NHCH_2} = 5.0, $J_{H4',H5'}$ = 5.0 Hz
22d	DMSO-d_6	1.37 (t, 3H, CH_2CH_3), 2.41 (s, 3H, COMe), 3.88 (d, 2H, NHCH_2), 4.41 (q, 2H, CH_2Me), 7.1-7.2 and 7.25-7.4 (broad, 2H, OH and NH), 7.28 (dd, 1H, $H_{5'}$), 8.38 (dd, 1H, $H_{4'}$), 8.63 (dd, 1H, $H_{6'}$), 9.22 (d, 1H, NHC*H*=), 9.55 (t, 1H, N*H*CH_2), 12.5 (d, 1H, N*H*CH=), J_{NHCH} = 11.5, J_{NHCH_2} = 5.1, J_{Et} = 7.08, $J_{H4',H5'}$ = 8.05, $J_{H4',H6'}$ = 1.7, $J_{H5',H6'}$ = 4.9 Hz
22e	DMSO-d_6	2.44 (s, 3H, Me), 3.89 (d, 1H, NHCH_2, 7.08 and 7.45 (broad, 2H, OH, NH), 7.7 (dd, 1H, $H_{5'}$), 7.85 (dd, 1H, $H_{4'}$), 9.01 (dd, 1H, $H_{6'}$), 9.05 (d, 1H, NHC*H*=), 9.65 (t, 1H, N*H*CH_2), 12.63 (d, 1H, N*H*CH=), J_{NHCH} = 11.4, J_{NHCH_2} = 5.4, $J_{H4',H5'}$ = 8.9, $J_{H5',H6'}$ = 4.1, $J_{H4',H6'}$ = 1.0 Hz
22a	DMSO-d_6	2.32 and 2.38 (s, 6H, COMe and Het-Me), 3.87 (d, 2H, NHCH_2), 7.01 (d, 1H, $H_{5'}$), 7.18 (s, 1H, $H_{3'}$), 7.0-7.2 and 7.25-7.4 (broad, 2H, NH, OH), 8.23 (d, 1H, $H_{6'}$), 8.98 (d, NHC*H*=), 9.69 (t, 1H, N*H*CH_2), 12.52 (d, 1H, N*H*CH=), J_{NHCH} = 12.0, J_{NHCH_2} = 5.07, $J_{H5',H6'}$ = 5.08 Hz
22i	deuteriochloroform	2.43 and 2.46 (s, 9H, 3 Me), 4.04 (d, 2H, NHCH_2), 5.16 and 6.15 (2s, 2H, OH and NH), 6.76 (s, 1H, $H_{5'}$), 9.11 (d, 1H, NHC*H*=), 9.78 (t, 1H, N*H*CH_2), 11.6 (d, 1H, N*H*CH=), J_{NHCH} = 12.06, J_{NHCH_2} = 6.03 Hz

Method D.

Into a solution of the corresponding azidoacetamide **15** (1 mmole) in ethanol (10 ml) ammonia gas was bubbled during 1 hour. After evaporation of the solvent the product was crystallized from propyl ether.

Method E.

To a solution of the corresponding azidoacetamide **15** (3 mmoles) in methanol (30 ml) palladized carbon (15% by weight of 5%) was added. The mixture was shaken in an atmosphere of hydrogen at 3.4 atmospheres for 1.5 hours. Upon filtration and evaporation of the solvent a mixture of two products was obtained and was separated by crystallization from propyl ether.

Method F.

A solution of the corresponding azidoacetamide **15** (5 mmoles) in methanol (50 ml) was treated with palladized carbon (15% by weight of 10%) and an 8 fold excess of ammonium formate. The reaction mixture was stirred for 2.5-3 hours and the progress of the reaction was monitored by tlc chromatography. The catalyst was filtered and the solvent evaporated to give a mixture of reaction products which was separated by crystallization from propyl ether.

The obtained products and their analytical data are collected in Table 7. The ^{1}H nmr data are presented in Table 8.

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