# Heterocyclic Amino Acids as Synthons. Reactions with Dicarbonyl Compounds



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**Dedicated to the memory of Professor Roland K. Robins**

From some alkyl heteroarylglycinates and dicarbonyl compounds various heterocyclic systems are easily accessible. Transformations are described which lead to imidazo[1,5-*a*]pyridines, heteroaryl-substituted pyrroles, pyrido[1,2-*a*]pyrazines, pyrido[1,2-*a*]pyrimidines or quinolizin-4-ones.

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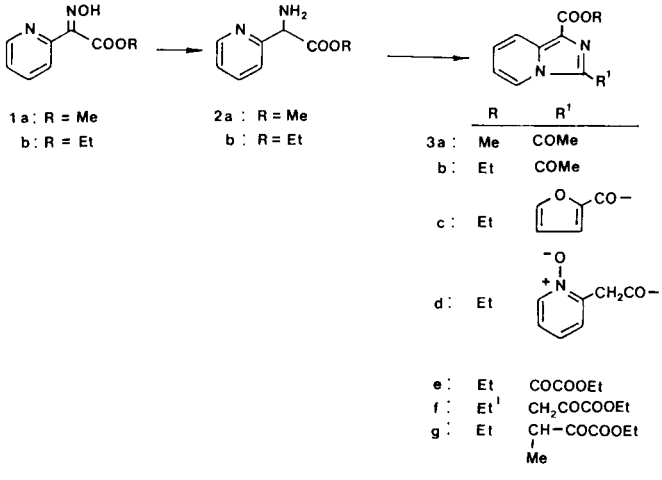
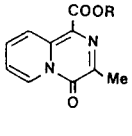
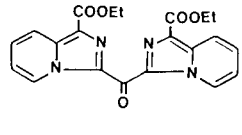
In our recent studies we have developed various approaches for the synthesis of heterocyclic amino acids. These and related compounds can be used for the preparation of various heterocyclic systems [1-3]. This communication deals with the preparation of various heteroarylglycines and their transformations into several heterocyclic systems.

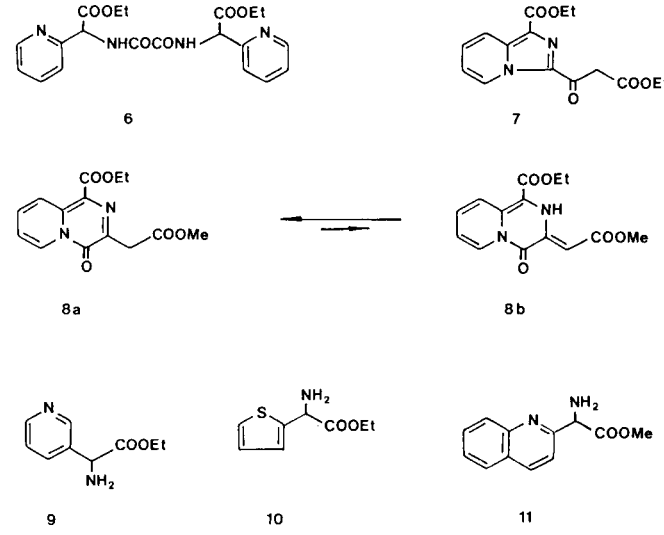
For the preparation of heterocyclic amino acids, usually methods different from the classic syntheses have to be employed. A convenient approach is to start from heteroarylacetic acids or their derivatives. For example, esters of 2-pyridylacetic acid are easily nitrosated to afford the corresponding oximes (or hydroxyimino derivatives) **1**. In a similar manner, the 3-pyridyl-, 2-quinolinyl- and 2-thienyl analogs have been prepared. Catalytic hydrogenation afforded the corresponding arylglycinates **2, 9, 11** [1] and the thienyl analog **10** was obtained by reduction with zinc and formic acid.



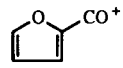
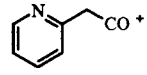
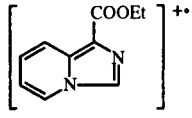
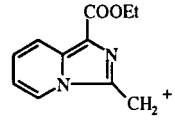
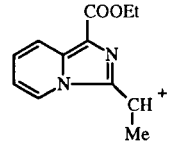




The obtained heteroarylglycines were used for transformations with dicarbonyl compounds. With various 2-ketoesters they were transformed into the corresponding imidazo[1,5-*a*]pyridines (**3**). There are only few synthetic approaches for this heterocyclic system and recently we have shown that some derivatives could be formed by using *N,N*-dimethylformamide- or acetamide acetals [1] as an one carbon reagent for cyclization. The structure of the obtained products was carefully investigated since two different ways of cyclization are possible. For example, the pyridylglycinate **2** could react with ethyl pyruvate to give either the corresponding 1-alkoxycarbonyl-3-acetylimidazo[1,5-*a*]pyridines **3a, 3b** or an 1-alkoxycarbonyl-3-methylpyrido[1,2-*a*]pyrazin-4-one **4**, depending on the initial




condensation of the amino group with either the ester or carbonyl group. The structural problem could be solved by nmr and mass spectroscopy. The mass spectrum revealed the presence of an fragment ion m/z = 43 and an analysis of this ion by application of the secondary mass spectrometry (MIKES) revealed that the fragment corresponds to the acetyl ion ($MeCO^+$). The same could be established for

Table 1
High resolution mass spectrometric identification of some acyl fragment ions

| Compound | Fragment ion (m/e) | Relative intensity (%) | m/z Calcd. | m/z Found | Structure of the radical ion |
|---|---|---|---|---|---|
| **3c** | 95 | 32 | 95.0132 | 95.0133 |  |
| **3d** | 120 | 62 | 120.0431 | 120.0449 |  |
| **3e** | 190 | 100 | 190.0723 | 190.0742 |  |
| **3f** | 203 | 68 | 203.0821 | 203.0818 |  |
| **3g** | 217 | 98 | 217.0912 | 217.0977 |  |

other condensation products **3** and high resolution mass spectrometric identification of some acyl fragment ions are presented in Table 1. Also a chemical test for the presence of methyl ketones with sodium nitroferricyanide [4] was positive. In order to eventually synthesize the elusive heterocycle **4**, the reaction was conducted under varying conditions such as boiling glacial acetic acid or in polyphosphoric acid at 80°. In no case compound **4** was formed. Also with diethyl mesoxalate only **3e** was formed although besides the possible bicycle **4** a bis-condensation product **5** is theoretically possible.

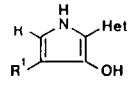
The product **3e**, itself being a 2-keto ester, did not react further with **2** to give **5**. The reaction of **2** with diethyl oxalate was also an exception and only the oxamide **6** could be isolated.

From the reaction of glycinate **2** and 2-keto esters the 3-acyl derivatives of imidazo[1,5-*a*]pyridines are thus available in a direct synthetic approach. So far, such compounds were prepared only as acetyl or benzoyl derivatives by the Friedel-Crafts reaction [5,6]. Diethyl oxalacetate or oxalpropionate could afford two different imidazo-[1,5-*a*]pyridines depending on which ester group may react. Analysis (tlc) of the reaction mixture revealed the presence of only one product and its structure could be established because of the high resolution mass spectrometry of fragment ions. In the case of the compound **3f** the fragment of m/z = 203 was found to be $C_{11}H_{11}N_2O_2^+$ what corresponds to 1-carbethoxyimidazo[1,5-*a*]pyridylmethyl ion which can be generated only from a compound having the structure of **3f** and not **7**. The same holds also for compound **3g** (see also Table 1). These results indicate that in the condensation reaction the ester group which is not adjacent to the carbonyl one is involved in the cyclization.

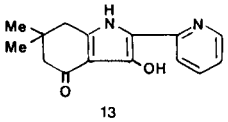
Since from the glycinate **2** the pyrido[1,2-*a*]pyrazine system **4** was not formed we have tried the transformation with dimethyl acetylenedicarboxylate (DMAD) in benzene. The product which was easily formed is compound **8**. It may be formed by initial addition of the amino group on the triple bond, followed by cyclization. From the $^1H$ nmr spectrum it follows that the compound exists in solution completely in the imine form **8a** and not in the tautomeric enamine form **8b**. Since there are only few reported syntheses of this bicyclic system [7] the present approach represents a new possibility.

Transformations of heteroarylglycinates with 1,3-dicarbonyl compounds were also of interest. It is known that ethyl glycinate or the esters of related amino acids react with ethyl acetoacetate to give the corresponding enamines [8]. The enamine when treated with sodium ethoxide was transformed into a mixture of two isomeric pyrroles [9]. 1,3-Dicarbonyl compounds react also with alkali salts of amino acids to form *N*-substituted amino acids (Dane salts) [10] used in the syntheses of peptides and penicillines [11-13].

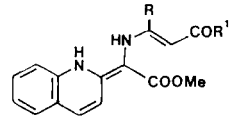
We have used as starting material heteroarylglycinates **2a**, **2b**, **9**, **10** and **11** and as 1,3-dicarbonyl compounds ethyl acetoacetate, acetylacetone and diethyl 1,3-acetone-



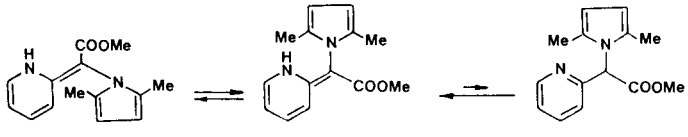
| | Het | R | $R^1$ |
|---|---|---|---|
| 12 a: | 3-pyridyl | Me | COOEt |
| b: | 2-thienyl | Me | COOEt |
| c: | 3-pyridyl | Me | COMe |
| d: | 2-thienyl | Me | COMe |
| e: | 3-pyridyl | $CH_2COOEt$ | COOEt |
| f: | 2-thienyl | $CH_2COOEt$ | COOEt |
| g: | 2-pyridyl | Me | COMe |
| h: | 2-pyridyl | $CH_2COOEt$ | COOEt |
| i: | 2-pyridyl | Me | COOEt |
| j: | 2-quinolyl | Me | COOEt |



13



| | R | $R^1$ |
|---|---|---|
| 14 a: | Me | OEt |
| b: | Me | Me |
| c: | $CH_2COOEt$ | OEt |



15c 15a 15b

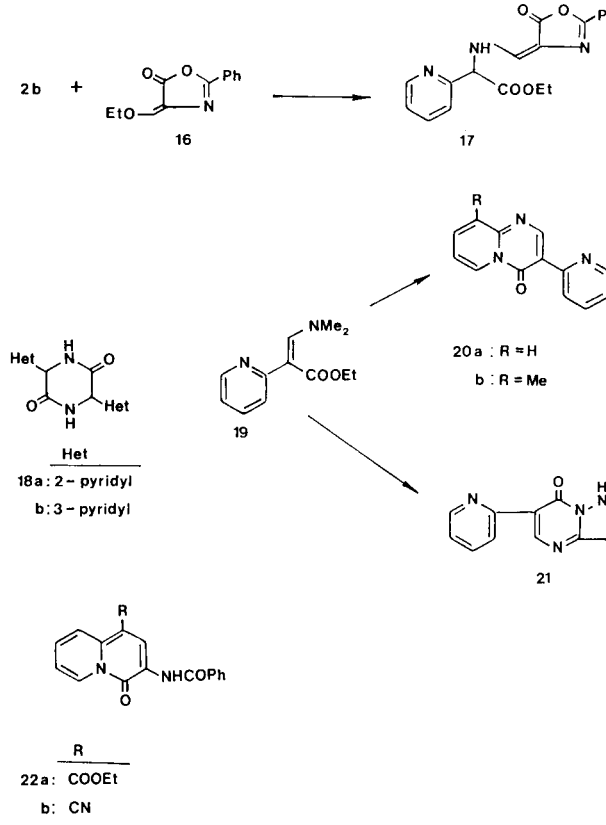
dicarboxylate. Compounds **9** and **10** were transformed in boiling ethanol in good yield into the corresponding enamines which were immediately transformed in the presence of sodium ethoxide into the corresponding pyrrole derivatives **12a-12f**. From **2b** the corresponding **12g** and **12h** derivatives were prepared whereas with 5,5-dimethyl-1,3-cyclohexanedione a tetrahydroindole derivative **13** was obtained. It is worthwhile to mention that from **2a** and ethyl acetoacetate the pyrrole **12i** was formed directly indicating that the basic pyridine ring nitrogen may also serve to induce cyclization of the initially formed enamine. A similar case has been observed with DMF [14].

From the reaction between **11** and 1,3-dicarbonyl compounds crystalline enamines **14a-c** were isolated. All compounds exist as presented, *i.e.* with an exocyclic double bond as evidenced from the $^1$H nmr spectra. So far, we have no evidence if the configuration about the double bonds is *E* or *Z*. Further cyclization to give pyrroles was successful only in the case of **14a** from which the pyrrole **12j** was obtained. The above results show that the new approach for the synthesis of substituted pyrroles is particularly suitable in the case where 2-heteroarylsubstituted pyrroles are the strategic goal.

In addition, we would like to report on some transformations in which heteroarylglycinates function as nucleophilic compounds. Compound **2a** reacted with a 1,4-dicarbonyl compound *i.e.* 2,5-hexanedione, to give the *N*-alkylated pyrrole **15**. As in the case of **14** the product exists entirely in the tautomeric form with an exocyclic double bond **(15a)** as evidenced from $^1$H nmr spectrum. In addition, there are two sets of signals for singlets of both methyl groups at the pyrrole ring and two singlets of the ester methyl group in a ratio of 1:2,3-2.5. From this the conclusion is reached that the pyrrole **15** exists of two configurations, **15a** and **15c**.

With oxazolinone **16** compound **2b** yielded **17**. Heteroarylglycinates **2b** and **9** afforded in boiling diglyme the corresponding 2,4-diketopiperazines **18a** and **18b**. Both compounds are analogs of the natural antibiotic 593A [15], but it should be mentioned that the dimerization as applied above has not been successful in the preparation of the antibiotic from 2-(3′-chloropyridyl-2′)glycine [16].

Finally, we would like to report on some syntheses of pyrido[1,2-*a*]pyrimidines and quinolizin-4-ones. The first mentioned system was prepared from **19** [17] and 2-aminopyridines to give **20a** and **20b**. On the other hand 3-amino-1,2,4-triazole afforded the corresponding 1,2,4-triazolo-



2b + 16 17

19

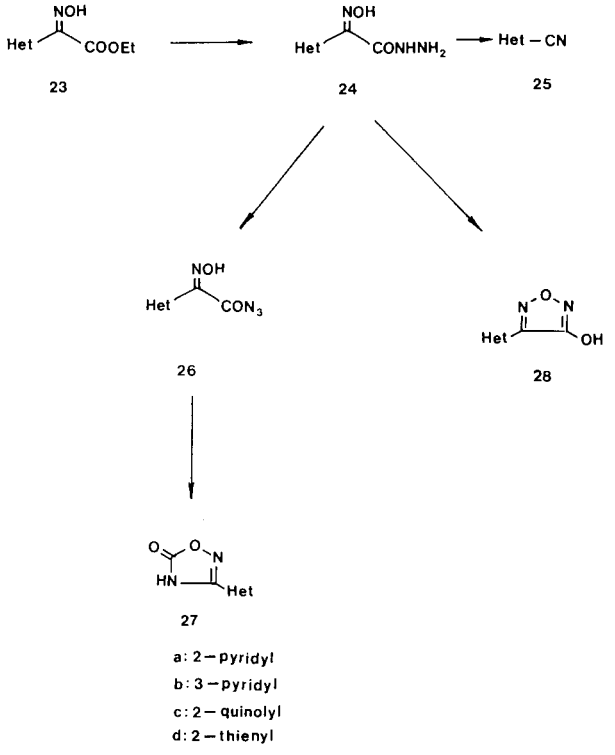
20a : R = H
b : R = Me

Het
18a : 2-pyridyl
b : 3-pyridyl

21

R
22a : COOEt
b : CN

[1,5-*a*]pyrimidine derivative **21**. From ethyl 2-pyridylacetate or 2-pyridylacetonitrile and **16** the quinolizin-4-ones **22a** and **22b** were obtained.




In our previous publication we have reported on the syntheses of 1,2,4- and 1,2,5-oxadiazoles from hydroxyimino heteroarylglycinates [1]. Upon nitrosation of the hydrazides **24** various products are formed. From **24a** only **26a** is formed whereas compound **24c** is in 5 minutes at 0° transformed exclusively into **28c**. From **24b** neither **26** nor **28** are formed, but the only product of thermal decomposition is the cyano compound **25b**. On the other hand, the isolated azide **26a** is thermally transformed exclusively into **27a** [1]. The thienyl analog **24d** upon nitrosation formed a thermally unstable azide **26d** which upon heating in chloroform gave only the 1,2,4-oxadiazole derivative **27d**. This is comparable to the behaviour of **26a**.

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The $^1$H nmr spectra were obtained on a Varian 360L (60 MHz) and Varian XL VXR-300 spectrometer (300 MHz) with TMS as internal standard. Infrared spectra were recorded on a Perkin-Elmer 727B spectrometer. Low resolution mass spectra were recorded with an CEC-21-110B and VG Analytical Autospec Q spectrometer at 70 eV and high resolution mass spectra were recorded on a VG Autospec Q spectrometer. Microanalyses were obtained on a Perkin-Elmer Analyzer model 2400. The progressing reactions were followed by tlc on silicagel using Fluka tlc-Silikagel 60778 plates and as mobile phase chloroform and methanol (7:3) or petroleum ether and ethyl acetate (7:3) were used.

Diethyl oxalacetate was prepared from its sodium salt (Fluka) after treatment with hydrochloric acid and extraction with chloroform. Diethyl mesoxalate, diethyl oxalpropionate and (2-furyl)glyoxylic acid (α-oxo-2-furanacetic acid) were purchased from Fluka. The ethyl ester of the last mentioned compound was prepared in the usual manner by acid catalyzed esterification with ethanol [18]. Ethyl 3-(*N*-oxidopyridyl-2')-2-oxopropionate was prepared according to the procedure as described in the literature [19].

Methyl 2-Hydroxyimino-2-(pyridyl-2')acetate (**1a**).

To a solution of methy 2-pyridylacetate (30.6 g, 0.2 mole) in glacial acetic acid (50 ml) at 0° with stirring an aqueous solution of sodium nitrite (14.0 g, 0.2 mole in 40 ml) was added portionwise. After addition was complete stirring was continued for 40 minutes at room temperature, water (100 ml) was added and the mixture was stirred for an additional 1 hour. The separated product was filtered, washed with water and dried. The colourless crude material (32.68 g, 90%) was crystallized from methanol, mp 99-102°; $^1$H nmr (DMSO-$d_6$): δ 7.24 (m, $H_5$), 7.66 (m, $H_3$, $H_4$), 8.08 (m, $H_6$), 3.68 and 3.70 (two s, COOMe), 12.28 (broad s, OH). from the presence of two singlets for the methyl group it may be concluded that the compound exists in two forms with regard to the orientation of the hydroxy and methoxycarbonyl groups. Because of small difference in chemical shifts it is not possible to determine exactly the ratio of both signals.

*Anal.* Calcd. for $C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.58; H, 4.53; N, 15.67.

Methyl 2-(2'-pyridyl)glycinate (**2a**).

The compound was obtained from **1a** according to a procedure described for its ethyl analog [20] in 81% yield as a pale yellow oil. It was used immediately for further transformations.

3-Acetyl-1-methoxycarbonylimidazo[1,5-*a*]pyridine (**3a**).

A solution of **2a** (1.66 g, 10 mmoles) in methanol (3 ml) was treated with ethyl pyruvate (1.2 g, 10.33 mmoles) and the mixture was heated under reflux for 20 minutes. During heating the product started separating and upon cooling the reaction mixture the product was filtered and crystallized from methanol and then from di-*n*-propyl ether, mp 174-176° (1.55 g, 71% yield) $^1$H nmr (deuteriochloroform): δ 2.63 (s, COMe), 3.90 (s, COOMe), 7.08 (ddd, $H_6$), 7.47 (ddd, $H_7$), 8.74-9.06 (m, $H_5$, $H_8$), $J_{5,6} = J_{6,7} = 7.4$, $J_{6,8} = J_{5,7} = 1.5$, $J_{7,8} = 8.80$ Hz.

*Anal.* Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.69; H, 4.57; N, 13.00.

3-Acetyl-1-ethoxycarbonylimidazo[1,5-*a*]pyridine (**3b**).

This compound was prepared in essentially the same manner as described above for **3a**, but starting from the ethyl analog **2b** in 40% yield, mp 130-131° (from ethanol).

*Anal.* Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.68; H, 5.16; N, 12.02.

1-Ethoxycarbonyl-3-(2'-furoyl)imidazo[1,5-*a*]pyridine (**3c**).

This compound was prepared in a similar manner from ethyl 2-furylglyoxylate in 31% yield after 1 hour of heating under reflux an ethanolic solution, mp 177-179° (from ethanol); $^1$H nmr (deuteriochloroform): δ 1.52 (t, $COOCH_2CH_3$), 4.45 (q, $COOCH_2Me$), 6.46 (m, $H_6$), 7.14 (m, $H_7$), 7.34-7.69 (m, $H_{3'}$, $H_{4'}$, $H_{5'}$), 9.02 (m, $H_5$, $H_6$), $J_{Et} = 7.4$ Hz; high resolution ms: m/z = 95.0133 ($M^+$); Calcd.

95.0133.

*Anal.* Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.28; H, 4.18; N, 9.77.

1-Ethoxycarbonyl-3-[(1'-oxido-2'-pyridyl)acetyl]imidazo[1,5-*a*]pyridine (**3d**).

From ethyl 3-(1'-oxido-2'-pyridyl)-2-oxopropionate and **2b** in ethanol the compound was obtained in 33% yield after 4 hours of heating under reflux, mp 215-217° (from ethanol and thereafter from ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.30 (t, $COOCH_2CH_3$), 4.27 (q, $COOCH_2Me$), 4.52 (s, $CH_2$), 7.07-7.19 (m, 4H, Ar), 7.41 (m, 1H, Ar), 8.00 (m, 1H, Ar), 8.76-9.08 (m, 2H, Ar), $J_{Et}$ = 6.8 Hz; ms: (m/z) 325 ($M^+$, 30%), 309 (31%), 281 (39%), 207 (100%), 120 (62%), 105 (49%), 92 (86%), 78 (66%), 65 (37%); high resolution ms for ion m/z = 120 ($C_7H_6NO^+$): 120.0431; Calcd. 120.0449.

*Anal.* Calcd. for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.58; H, 4.69; N, 13.06.

Ethyl (1-Ethoxycarbonylimidazo[1,5-*a*]pyridin-3-yl)glyoxylate (**3e**).

It was prepared from diethyl mesoxalate and **2b** in boiling ethanol after 6 hours in 15% yield, mp 160-162° (from ethanol); $^1$H nmr (deuteriochloroform): δ 1.45 (t, two Me), 4.41 (q, two $COOCH_2Me$), 7.38 (ddd, $H_6$), 7.81 (ddd, $H_7$), 9.05-9.44 (m, $H_5$, $H_8$), $J_{Et}$ = 6.9, $J_{5,6}$ = $J_{6,7}$ = 7.6, $J_{6,8}$ = 1.7, $J_{5,7}$ = 1.4, $J_{7,8}$ = 8.8 Hz; ms: (m/z) 290 ($M^+$, 70%), 262 (44%), 217 (30%), 190 (100%), 144 (63%), 105 (79%), 78 (50%), 69 (75%), 57 (71%); high resolution ms for ion m/z = 190 ($C_{10}H_{10}N_2O_2^+$): 190.0742; Calcd. 190.0742.

*Anal.* Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.12; H, 4.89; N, 9.93.

Ethyl 3-(1'-Ethoxycarbonylimidazo[1,5-*a*]pyrid-3'-yl)-2-oxopropionate (**3f**).

The compound was obtained from **2b** and freshly prepared diethyl oxalacetate after heating for 7 hours. After standing two days at room temperature the separated crystals were filtered and crystallized from ethanol, mp 124-126° (8% yield); $^1$H nmr (deuteriochloroform): δ 1.32 (t, $COOCH_2CH_3$), 4.04 (s, $CH_2$), 4.40 (q, $COOCH_2Me$), 7.31 (m, $H_6$), 7.80 (m, $H_7$), 9.23 (m, $H_5$, $H_8$); $J_{Et}$ = 7.5 Hz; ms: (m/z) 304 ($M^+$, 35%), 231 (25%), 217 (9%), 203 (68%), 105 (26%), 97 (33%), 81 (50%), 69 (100%), 57 (69%); high resolution ms for ion m/z = 203 ($C_{11}H_{11}N_2O_2^+$): 203.0818; Calcd: 203.0820.

*Anal.* Calcd. for $C_{15}H_{16}N_2O_5$: C, 59.20; H, 5.30; N, 9.21. Found: C, 59.54; H, 5.35; N, 9.27.

Ethyl 3-(1'-Ethoxycarbonylimidazo[1,5-*a*]pyrid-3'-yl)-2-oxobutanoate (**3g**).

The compound was prepared from diethyl oxalpropionate and **2b** after heating for 6 hours. The product separated overnight at room temperature and was crystallized from ethanol, mp 93-95° (24% yield); $^1$H nmr (deuteriochloroform); δ 1.10-1.80 (m, 9H, two $COOCH_2CH_3$ and Me), 4.37 (q, two $COOCH_2Me$ and CHMe), 7.30 (ddd, $H_6$), 7.77 (ddd, $H_7$), 9.20 (m, $H_5$, $H_8$); $J_{Et}$ = $J_{CH,Me}$ = 6.6, $J_{5,6}$ = $J_{6,7}$ = 7.0, $J_{5,7}$ = 1.0, $J_{6,8}$ = 1.5, $J_{7,8}$ = 8.4 Hz; ms: (m/z) 318 ($M^+$, 66%), 245 (100%), 217 (98%), 171 (35%), 105 (39%), 78 (57%); high resolution ms for ion m/z = 217 ($C_{12}H_{13}N_2O_2^+$): 217.0912; Calcd: 217.0977.

*Anal.* Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.28; H, 5.55; N, 8.53.

Bis[1-Ethoxycarbonyl-1-(2'-pyridyl)methyl]-1,1-oxamide (**6**).

A mixture of **2b** (1.80 g, 10 mmoles), ethanol (4 ml) and diethyl oxalate (1.50 g, 10.2 mmoles) was heated under reflux for 4 hours. The reaction was left overnight at room temperature and the separated product was filtered and crystallized from ethanol to give **6**, mp 195-197° (0.11 g, 5% yield); $^1$H nmr (deuteriochloroform): δ 1.14 (t, $COOCH_2CH_3$), 4.10 (q, $COOCH_2Me$), 5.50 (d, CHNH), 6.97-7.75 (m, $H_3$, $H_4$, $H_5$), 8.40 (m, $H_6$), 8.70 (d, CH-NH), $J_{Et}$ = 6.8, $J_{CHNH}$ = 6.5, $J_{5,6}$ = 5.8 Hz; ir: 3350 (NH), 1740 (CO), 1660 (CO) $cm^{-1}$.

*Anal.* Calcd. for $C_{20}H_{22}N_4O_6$: C, 57.96; H, 5.35; N, 13.52. Found: C, 58.25; H, 5.25; N, 13.84.

Methyl (1-Ethoxycarbonyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrazin-3-yl)acetate (**8**).

To a solution of **2b** (2.10 g, 11.67 mmoles) in dry benzene (7 ml) dimethyl acetylenedicarboxylate (1.66 g, 11.68 mmoles) was added portionwise. During the addition heat is evolved and the reaction mixture was then heated under reflux for 1 hour. Upon evaporation *in vacuo* the oily residue was treated with a few ml of ethanol and the mixture was left aside for three days. The formed crystals were separated and crystallized from a mixture of *n*-hexane and benzene, mp 157-159° (0.855 g, 25% yield); $^1$H nmr (deuteriochloroform): δ 1.45 (t, $COOCH_2CH_3$) 3.66 (s, COOMe), 4.02 (s, $CH_2$), 4.44 (q, $COOCH_2Me$), 7.01-7.78 (m, $H_7$, $H_8$), 8.84-9.22 (m, $H_6$, $H_9$), $J_{Et}$ = 6.9 Hz; ms: (m/z) 290 ($M^+$, 74%), 262 (15%), 231 (27%), 203 (100%), 175 (16%), 131 (33%), 105 (27%).

*Anal.* Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 58.34; H, 4.67; N, 9.62.

Ethyl 2-Hydroxyimino-2-(2'-thienyl)acetate (**23d**).

A solution of ethanolic sodium ethoxide (prepared from 2.3 g of sodium and 50 ml of absolute ethanol) was treated with diethyl ether (80 ml), cooled to 0° and with stirring ethyl 2-thienylacetate (17.0 g, 0.1 mmole) was added. To the stirred reaction mixture during 30 minutes isoamyl nitrite (23.5 g, 0.2 mmole) was added by keeping the reaction mixture at 5-10°. After addition was complete stirring was continued for 3 hours, water (50 ml) was added and the reaction mixture was acidified with glacial acetic acid to *p*H 5. The resulting solution was stirred for 1 hour, the organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic phases were dried and evaporated under *vacuo*. The solid residue was treated with *n*-hexane, filtered and washed with *n*-hexane. The crude product was crystallized from a mixture of *n*-hexane and benzene, mp 125-127° (8.02 g, 40% yield); $^1$H nmr (DMSO-$d_6$): δ 1.35 (t, $COOCH_2CH_3$), 4.26 (q, $COOCH_2Me$), 7.03 (dd, $H_4$), 7.68 (m, $H_3$, $H_5$), 10.64-11.81 (broad s, OH), $J_{Et}$ = 6.8, $J_{3,4}$ = $J_{4,5}$ = 3.8 Hz.

*Anal.* Calcd. for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03. Found: C, 48.47; H, 4.60; N, 7.11.

Ethyl 2-(2'-Thienyl)glycinate (**10**).

The above hydroxyimino derivatives **23d** (2.10 g, 10.54 mmoles) was dissolved in ethanol (10 ml) for formic acid (20 ml of 50%). With stirring at 15-20° finely powdered zinc (2.50 g) was added portionwise during 6 hours. Stirring was continued for 2 hours, the reaction mixture was filtered, the residue washed with ethanol and the solution was evaporated *in vacuo*. The residue was treated with water (5 ml), the solution was neutralized with solid sodium carbonate to *p*H 7 and the mixture was extracted with chloroform. The dried extracts were evaporated to give a pale yellow oil (1.78, 91% yield) which slowly darkened when exposed to air. The product was immediately used for further transformations; $^1$H nmr (deuteriochloroform): δ 1.24 (t, $COOCH_2CH_3$), 2.38 (broad s, $NH_2$), 4.11 (q, $COOCH_2Me$), 4.68 (s, CHNH),

6.62-7.07 (m, Ar), $J_{Et}$ = 6.3 Hz.

General Procedure for the Preparation of 4,5-Disubstituted 2-(Heteroaryl)-3-hydroxypyrroles from Esters of Heteroarylglycinates and 1,3-Dicarbonyl Compounds.

A solution of the corresponding alkyl heteroarylglycinate (10 mmoles) in ethanol (5 ml) was treated with a 1,3-dicarbonyl compound (10 mmoles) and the reaction mixture was heated under reflux for 3-4 hours until the presence of the glycinate was not more detected by tlc. The reaction mixture was evaporated *in vacuo* and the oily residue was dissolved in ethanol (4-5 ml of absolute), a solution of sodium ethoxide (prepared from 10 mmoles of sodium and 3 ml of ethanol) was added and the reaction mixture was heated under reflux for 45-120 minutes. The cooled mixture was neutralized with 10% acetic acid until *p*H 5-6. After scratching, the product separated, it was filtered and crystallized from the particular solvent. In this manner the following derivatives were obtained:

4-Ethoxycarbonyl-3-hydroxy-5-methyl-2-(pyridyl-3')pyrrole (**12a**).

Ethyl acetoacetate and **9** were used as starting compounds. The product was formed in 22% yield, mp 219-221° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 1.14 (t, $COOCH_2CH_3$), 2.46 (s, Me), 4.22 (q, $COOCH_2Me$), 7.24 (dd, $H_{5'}$), 7.73-8.41 (m, $H_{2'}$, $H_{4'}$, $H_{6'}$), 8.77 (broad s, OH), 11.11 (broad s, NH), $J_{Et}$ = 6.8, $J_{4',5'}$ = 8.0, $J_{5',6'}$ = 5.2 Hz.

*Anal.* Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.57; H, 5.67; N, 11.16.

4-Ethoxycarbonyl-3-hydroxy-5-methyl-2-(2'-thienyl)pyrrole (**12b**).

The compound was obtained from ethyl acetoacetate and **10** in 67% yield, mp 174-178° (from aqueous ethanol); $^1$H nmr (DMSO-$d_6$): δ 1.23 (t, $COOCH_2CH_3$), 2.34 (s, Me), 4.17 (q, $COOCH_2Me$), 6.74-7.23 (m, Ar), 8.01 (s, OH), 11.30 (broad s, NH), $J_{Et}$ = 6.8 Hz.

*Anal.* Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.76; H, 4.95; N, 5.81.

4-Acetyl-3-hydroxy-5-methyl-2-(3'-pyridyl)pyrrole (**12c**).

The compound was prepared from acetylacetone and **9** in 11% yield, mp 241-243° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 2.38 and 2.48 (two s, Me, COMe), 7.17 (dd, $H_{5'}$), 7.85 (ddd, $H_{4'}$), 8.07 (dd, $H_{6'}$), 9.78 (broad s, OH), 11.06 (broad s, NH), $J_{2',4'}$ = $J_{4',6'}$ = 2.3, $J_{4',5'}$ = 7.7, $J_{5',6'}$ = 4.2 Hz.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 67.01; H, 5.43; N, 13.12.

4-Acetyl-3-hydroxy-5-methyl-2-(2'-thienyl)pyrrole (**12d**).

Acetylacetone and **10** were used as starting compounds. The product was obtained in 36% yield, mp 200-205° (from a mixture of benzene and ethanol); $^1$H nmr (DMSO-$d_6$): δ 2.37 and 2.47 (two s, Me and COMe), 6.62-7.18 (m, Ar), 9.23 (broad s, OH), 10.96 (broad s, NH).

*Anal.* Calcd. for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33. Found: C, 59.32; H, 4.73; N, 6.26.

4-Ethoxycarbonyl-5-ethoxycarbonylmethyl-3-hydroxy-2-(3'-pyridyl)pyrrole (**12e**).

It was synthesized from diethyl 1,3-acetonedicarboxylate and **9** in 21% yield, mp 183-185° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 1.21 (t, $COOCH_2CH_3$), 3.81 (s, $CH_2$), 4.14 (q, $COOCH_2Me$), 7.23 (dd, $H_{5'}$), 7.88 (m, $H_{4'}$), 8.21 (m, $H_{2'}$, $H_{6'}$), 8.79 (broad s, OH), 11.33 (broad s, NH), $J_{Et}$ = 6.8, $J_{5',6'}$ = 4.9, $J_{4',5'}$ = 8.8 Hz.

*Anal.* Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.30; H, 5.53; N, 8.85.

4-Ethoxycarbonyl-5-ethoxycarbonylmethyl-3-hydroxy-2-(2'-thienyl)pyrrole (**12f**).

The compound was prepared from diethyl 1,3-acetonedicarboxylate and **10** in 22% yield, mp 99-101° (from a mixture of benzene and *n*-hexane); $^1$H nmr (DMSO-$d_6$): δ 1.22 (t, $COOCH_2CH_3$), 3.76 (s, $CH_2$), 4.08 (q, $COOCH_2Me$), 6.72-7.23 (m, Ar), 8.00 (s, OH), 11.19 (broad s, NH), $J_{Et}$ = 6.7 Hz.

*Anal.* Calcd. for $C_{15}H_{17}NO_5S$: C, 55.71; H, 5.30; N, 5.33. Found: C, 55.71; H, 5.09; N, 4.46.

4-Acetyl-3-hydroxy-5-methyl-2-(2'-pyridyl)pyrrole (**12g**).

The compound was obtained from acetylacetone and **2a** in 34% yield, mp 230-233° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 2.39 and 2.52 (two s, Me and COMe), 6.96 (ddd, $H_{5'}$), 7.32-7.86 (m, $H_{3'}$, $H_{4'}$), 8.33 (dd, $H_{6'}$), 11.40 (broad s, NH), $J_{4',5'}$ = $J_{5',6'}$ = 6.8, $J_{3',5'}$ = 1.9, $J_{4',6'}$ = 1.6 Hz.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.71; H, 5.46; N, 12.73.

4-Ethoxycarbonyl-5-ethoxycarbonylmethyl-3-hydroxy-2-(2'-pyridyl)pyrrole (**12h**).

It was prepared from diethyl 1,3-acetonedicarboxylate and **2a** in 25% yield, mp 136-138° (from ethanol); $^1$H nmr (DMSO-$d_6$): δ 1.26 (t, $COOCH_2CH_3$), 3.81 (s, $CH_2$), 4.06 (q, $COOCH_2Me$), 6.90 (ddd, $H_{5'}$), 7.52 (m, $H_{3'}$, $H_{4'}$), 8.26 (m, $H_{6'}$), 9.13 (broad s, OH), 11.36 (broad s, NH), $J_{Et}$ = 6.8, $J_{3',5'}$ = 1.9, $J_{4',5'}$ = 8.1, $J_{5',6'}$ = 5.8 Hz.

*Anal.* Calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.39; H, 5.70; N, 8.81.

4-Ethoxycarbonyl-3-hydroxy-5-methyl-2-(2'-pyridyl)pyrrole (**12i**).

A solution of **2a** (1.60 g, 9.63 mmoles) in methanol (3 ml) was treated with ethyl acetoacetate (1.60 g, 12.29 mmoles) and the reaction mixture was heated under reflux for 3 hours. After evaporation *in vacuo* an oily and partially crystalline product remained to which methanol (2 ml) and diethyl ether (2 ml) were added. Upon scratching more crystals separated and the mixture was left aside two days. The crystals were separated and crystallized from methanol and thereafter from ethyl acetate, mp 183-186° (0.37 g, 16%); $^1$H nmr (deuteriochloroform): δ 1.31 (t, $COOCH_2CH_3$), 2.32 (s, Me), 4.23 (q, $COOCH_2Me$), 6.99 (ddd, $H_{5'}$), 7.23-7.76 (m, $H_{3'}$, $H_{4'}$), 8.08 (dd, $H_{6'}$), 8.39 (broad s, OH), 9.48 (broad s, NH), $J_{Et}$ = 6.8, $J_{3',5'}$ = 1.6, $J_{4',5'}$ = $J_{5',6'}$ = 5.8 Hz.

*Anal.* Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.54; H, 5.65; N, 11.60.

4-Ethoxycarbonyl-3-hydroxy-2-(2'-quinolyl)-5-methylpyrrole (**12j**).

To a boiling solution of the enamine **14a** (0.56 g, 1.7 mmoles) in ethanol (5 ml) an ethanolic solution of sodium ethoxide (prepared from 0.12 g sodium and 3 ml of ethanol) was added and the reaction mixture was heated under reflux for 90 minutes. Upon cooling the reaction mixture was neutralized with acetic acid (10 ml of 10%) under vigorous stirring. Water (5 ml) was added and the crude red product was filtered, washed with water and crystallized from ethanol to give the product, mp 215-217° (0.22 g, 44% yield); $^1$H nmr (deuteriochloroform): δ 1.28 (t, $COOCH_2CH_3$), 2.23 (s, Me), 4.26 (q, $COOCH_2Me$), 7.11-7.90 (m, Ar), 8.00 (s, OH), $J_{Et}$ = 6.9 Hz; high resolution ms: (m/z) 296.1198 ($M^+$), Calcd: 296.1160.

6,6-Dimethyl-3-hydroxy-4-oxo-2-(2′-pyridyl)-4,5,6,7-tetrahydroindole (**13**).

A solution of **2b** (1.80 g, 10 mmoles) in ethanol (7 ml) was treated with 5,5-dimethyl-1,3-cyclohexanedione (1.40 g, 10 mmoles) and the reaction mixture was heated under reflux for 8 hours. Upon evaporation *in vacuo* to dryness a dark red oily residue was dissolved in ethanol (4 ml) and treated with a solution of sodium ethoxide (prepared from 0.23 g of sodium and 5 ml ethanol). The reaction mixture was heated under reflux for 2 hours, cooled and neutralized under stirring with acetic acid (10 ml of 10%). The separated product was filtered, washed with water and ethanol and crystallized from ethanol to give compound **13**, mp 247-249° (0.54 g, 21%); $^1$H nmr (DMSO-$d_6$): δ 1.06 (s, two Me), 2.16 (s, two $H_7$), 2.65 (s, two $H_5$), 6.90 (ddd, $H_{5'}$), 7.35-7.84 (m, $H_{3'}$, $H_{4'}$), 8.29 (dd, $H_{6'}$), 9.81 (broad s, OH), 11.23 (broad s, NH), $J_{4',5'}$ = 7.7, $J_{3',5'}$ = 1.9, $J_{4',6'}$ = 1.5, $J_{5',6'}$ = 5.8 Hz.

*Anal.* Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.79; H, 6.33; N, 10.90.

General Procedure for the Preparation of Enamines from Methyl 2-(2′-Quinolinyl)glycinate and 1,3-Dicarbonyl Compounds.

The quinoline amino acid **11** (5 mmoles), methanol (3-5 ml) and the corresponding 1,3-dicarbonyl compound (5 mmoles) were heated under reflux for 3 hours. Upon cooling the separated product was filtered, washed with some ethyl acetate and crystallized.

In this manner the following compounds were prepared.

Ethyl 3-*N*-[1′-(2″-Quinolilidene)-1′-methoxycarbonylmethyl]amino-2-butenoate (**14a**).

The compound was prepared from **11** and ethyl acetoacetate in 64% yield, mp 127-129° (from methanol); $^1$H nmr (deuteriochloroform): δ 1.29 (t, $COOCH_2CH_3$), 1.71 (s, Me), 3.32 (s, COOMe), 4.10 (q, $COOCH_2$Me), 4.61 (s, CH), 6.71-7.58 (m, Ar), 8.90 (broad s, NH), 12.32 (broad s, NH), $J_{Et}$ = 7.3 Hz; ir: 3270 and 3000 (NH), 1660 and 1600 (CO) cm$^{-1}$.

*Anal.* Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.84; H, 6.14; N, 8.53. Found: C, 65.67; H, 6.05; N, 8.48.

2-*N*-[1′-(2″-Quinolilidene)-1′-methoxycarbonylmethyl]aminopent-2-en-5-one (**14b**).

It was obtained from **11** and acetylacetone in 25% yield, mp 146-148° (from ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.73 (s, Me), 2.06 (s, COMe), 3.64 (s, COOMe), 5.03 (s, CH), 6.58-7.49 (m, Ar), 10.81 (broad s, NH), 12.53 (broad s, NH).

*Anal.* Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.59; H, 5.77; N, 9.05.

Diethyl [3-*N*-1′-(2″-Quinolilidene)-1′-methoxycarbonylmethyl]amino-2-penten-1,5-dioic Acid (**14c**).

Diethy 1,3-acetonedicarboxylate and **11** were used as starting material. The product was formed 46% yield, mp 135-138° (from ethyl acetate); $^1$H nmr (deuteriochloroform): δ 0.99 (t, $COOCH_2CH_3$), 2.90 and 2.96 (two s, $CH_2$), 3.04 (s, COOMe), 3.34 (q, $COOCH_2$Me), 4.57 (s, CH), 6.81-7.35 (m, Ar), 8.71 (broad s, NH), 11.89 (broad s, NH), $J_{Et}$ = 6.3 Hz.

*Anal.* Calcd. for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 62.47; H, 6.09; N, 7.21.

Methyl 2-(2′,5′-Dimethylpyrrol-1′-yl)-2-(2″-pyridyl)acetate (**15**).

A mixture of **2a** (1.66 g, 10 mmoles), methanol (3 ml) and 2,5-hexanedione (1.3 g, 11.4 mmoles) was heated under reflux for 5 hours. Upon cooling crystals separated, methanol (5 ml) was added and the product was filtered. The yellow-green compound was crystallized from ethanol, mp 140-143° (1.44 g, 59% yield); $^1$H nmr (deuteriochloroform): δ 1.96 and 2.10 (two s, two Me), 3.66 and 3.86 (two s, COOMe), 5.96 (s, and m, $H_3$, $H_4$, $H_{3'}$), 6.27 (ddd, $H_{5'}$), 6.91-7.73 (m, $H_{4'}$, $H_{6'}$), 13.69 (broad s, NH); $J_{3',5'}$ = 1.6, $J_{4',5'}$ = 8.3, $J_{5',6'}$ = 7.1 Hz, the ratio of signals at δ 1.96 and 2.0 = 2.3:1 and those at δ 3.66 and 3.86 = 2.5:1.

*Anal.* Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.59; H, 6.58; N, 11.49.

Ethyl *N*-Methylene-[4′-(2′-phenyl-5′-oxo-oxazolinyl]-2-(2″-pyridyl)-glycinate (**17**).

A mixture of **2b** (1.8 g, 10 mmoles), ethanol (15 ml) and **16** (2.17 g, 10 mmoles) was heated under reflux for 30 minutes. Upon cooling the separated product was filtered and crystallized from ethyl acetate, mp 177-181° (3.02 g, 86% yield); $^1$H nmr DMSO-$d_6$): δ 1.12 (t, $COOCH_2CH_3$), 4.07 (q, $COOCH_2$Me), 5.64 and 6.25 (m, CH-NH), 7.05-7.85 (m, Ar and C=CH-NH), 8.43 (m, $H_6$), 8.85 (broad s, CH-NH); $J_{Et}$ = 6.7, $J_{CHNH}$ = 5.8, $J_{5,6}$ = 6.0 Hz; ir: 3150 (NH), 1750 and 1640 (CO) cm$^{-1}$.

*Anal.* Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.23; H, 4.85; N, 11.55.

3,6-Bis(2′-pyridyl)piperazine-2,5-dione (**18a**).

A mixture of **2b** (1.8 g , 10 mmoles) and 2-methoxyethyl ether (1.5 ml) was heated under reflux for 7 hours and the separated product was filtered and crystallized twice from ethanol, mp 243-245° (upon melting new crystals were formed which had mp over 320°) (0.2 g, 15% yield); $^1$H nmr (DMSO-$d_6$): δ 5.03 (d, $H_3$, $H_6$), 7.18 (m, $H_{3'}$, $H_{5'}$), 7.60 (ddd, $H_{4'}$), 8.11-8.48 (m, $H_6$, and NH), $J_{CHNH}$ = 2.0, $J_{4',6'}$ = 1.9, $J_{3',4'}$ and $J_{4',5'}$ = 6.7 and 7.7 Hz.

*Anal.* Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.45; H, 4.32; N, 20.53.

3,6-Bis(3′-pyridyl)piperazine-2,5-dione (**18b**).

The compound was prepared in a similar manner as the above analog from **9** in 34% yield, mp >270° (because of its insolubility in common solvents the compound could not be crystallized and also a $^1$H nmr spectrum could not be taken).

*Anal.* Cacld. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.40; H, 4.42; N, 19.99.

9-Methyl-3-(2′-pyridyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**20b**).

A mixture of the dimethylaminomethylene compound **19** (0.98 g, 4.45 mmoles), glacial acetic acid (4 ml) and 2-amino-3-methylpyridine (0.54 g, 5 mmoles) was heated under reflux for 4 hours. Upon cooling the reaction mixture was evaporated *in vacuo*, some methanol was added and the solvent evaporated. This procedure was repeated several times. The oily residue was treated with water (2 ml) and neutralized with aqueous sodium hydrogen carbonate to *p*H 7. The crude yellow product was filtered, washed with water and ethanol and crystallized from ethanol, mp 147-148° (0.36 g, 34% yield); $^1$H nmr (deuteriochloroform): δ 2.67 (s, Me), 7.03-7.40 (m, 2H, Ar), 7.57-7.97 (m, 2H, Ar), 8.47-8.13 (m, 2H, Ar), 9.10-9.33 (m, 1H, Ar), 9.47 (s, $H_2$).

*Anal.* Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.51; H, 4.54; N, 17.68.

3-(2′-Pyridyl)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**20a**).

This compound was prepared in essentially the same manner as the above analog from 2-aminopyridine and **19** after 6 hours

heating in 36% yield, mp 158-161° (from a mixture of *n*-hexane and benzene); $^1$H nmr (deuteriochloroform): δ 6.78-7.06 (m, 3H, Ar), 7.26-7.63 (m, 2H, Ar), 8.08-8.42 (m, 2H, Ar), 8.77-8.93 (m, 1H, Ar), 9.02 (s, $H_2$).

*Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.94; H, 4.06; N, 18.83. Found: C, 69.84; H, 3.98; N, 18.56.

6-(2'-Pyridyl)-7-oxo-7*H*-1,2,4-triazolo[1,5-*a*]pyrimidine (**21**).

It was obtained from 3-amino-1,2,4-triazole using the procedure as described above for compound **20b** after heating the reaction mixture under reflux for 5 hours in 30% yield, mp >270° (from aqueous ethanol).

*Anal.* Calcd. for $C_{10}H_7N_5O$: C, 56.33; H, 3.31; N, 32.85. Found: C, 56.27; H, 3.05; N, 33.22.

3-Benzoylamino-1-ethoxycarbonyl-4-oxo-4*H*-quinolizine (**22a**).

The compound was prepared from ethyl pyridylacetate and **16** after 90 minutes heating under reflux according to the procedure described above for **20b** in 79% yield, mp 194-195° (from ethanol); $^1$H nmr (deuteriochloroform): δ 1.46 (t, $COOCH_2CH_3$), 4.24 (q, $COOCH_2Me$), 6.91 (ddd, $H_7$), 7.20-7.45 (m, 3H, of Ph and $H_8$), 7.58-7.87 (m, 2H of Ph), 8.73-9.04 (m, $H_6$, $H_9$, N*H*CO), 9.39 (s, $H_2$), $J_{Et}$ = 5.7, $J_{6,7}$ = $J_{6,8}$ = 6.7, $J_{7,9}$ = 1.0 Hz.

*Anal.* Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33. Found: C, 67.70; H, 4.64; N, 8.34.

3-Benzoylamino-1-cyano-4-oxo-4*H*-quinazoline (**22b**).

This compound was prepared according to the procedure as described for **22a** from 2-pyridylacetonitrile and **16** after 45 minutes under reflux in 68% yield, mp 233-235° (from ethanol); ir: 2200 (CN), 1620 and 1680 (CO) cm$^{-1}$.

*Anal.* Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53. Found: C, 70.40; H, 3.67; N, 14.56.

2-Hydroxyimino-2-(2'-thienyl)acetic Hydrazide (**24d**).

The corresponding ester (**23d**) (0.8 g, 4 mmoles) was dissolved in absolute ethanol (10 ml), hydrazine hydrate (1.6 g of 95%) was added and the reaction mixture was heated under reflux for 2.5 hours. Upon evaporation to dryness the residue was crystallized from ethanol, mp 204-206° (0.46 g, 62% yield); $^1$H nmr (DMSO-$d_6$): δ 4.44 (broad s, $NH_2$), 6.86 (dd, $H_4$), 7.62 (m, $H_3$, $H_5$), 9.33 (broad s, NH).

*Anal.* Calcd. for $C_6H_7N_3O_2S$: C, 38.91; H, 3.81; N, 22.69. Found: C, 38.97; H, 3.82; N, 23.11.

2-Hydroxyimino-2-(2'-thienyl-2')acetic Acid Azide (**26d**).

The above compound was transformed into the azide in the conventional manner in an acid solution with sodium nitrite in 89% yield. The crude product was washed with water and benzene, but because of its thermal instability crystallization was not successful, mp 106-115° dec and formation of new crystals with mp 188-193°; ir: 3100-3300 (OH), 2150 ($N_3$), 1700 (CO) cm$^{-1}$.

3-(2'-Thienyl)-1,2,4-oxadiazolin-5-one (**27d**).

The above azide (0.93 g, 5 mmoles) was suspended in hydrochloric acid (30 ml of 10%), the mixture was cooled to 0° and during 5 minutes an aqueous solution of sodium nitrite (0.35 g, 5.07 mmoles in 4 ml water) was added. Stirring was continued for 30 minutes, water (10 ml) was added and the mixture was neutralized with aqueous sodium carbonate (10%) to *p*H 7. After extraction with chloroform (4 times with 30 ml) the dried combined extracts were heated under reflux for 1 hour. The solvent was evaporated *in vacuo* almost to dryness, the product was filtered and washed with chloroform. It was crystallized from ethyl acetate, mp 203-206 (0.38 g, 45% yield); $^1$H nmr (DMSO-$d_6$): δ 7.24 (dd, $H_4$), 7.70 (dd, $H_3$), 7.90 (dd, $H_5$), 13.00 (broad s, NH), $J_{3,4}$ = 3.90, $J_{3,5}$ = 1.20, $J_{4,5}$ = 5.10 Hz.

*Anal.* Calcd. for $C_6H_4N_2O_2S$: C, 42.85; H, 2.40; N, 16.66. Found: C, 43.05; H, 2.28; N, 16.59.

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