Heterocycles from Amino Acids. A Novel Synthetic Approach for Imidazo[1,5-*a*]pyridines and Imidazo[1,5-*a*]quinolines

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From the corresponding heterocyclic amino acids **2** and **9a** the heterocyclic systems imidazo[1,5-*a*]pyridine (**3**) and imidazo[1,5-*a*]quinoline (**10**) are easily accessible. From compound **7** the tricyclic system **11** was prepared and from compound **17a** a pyridyl-1,2,4-triazinone (**18**) could be obtained.

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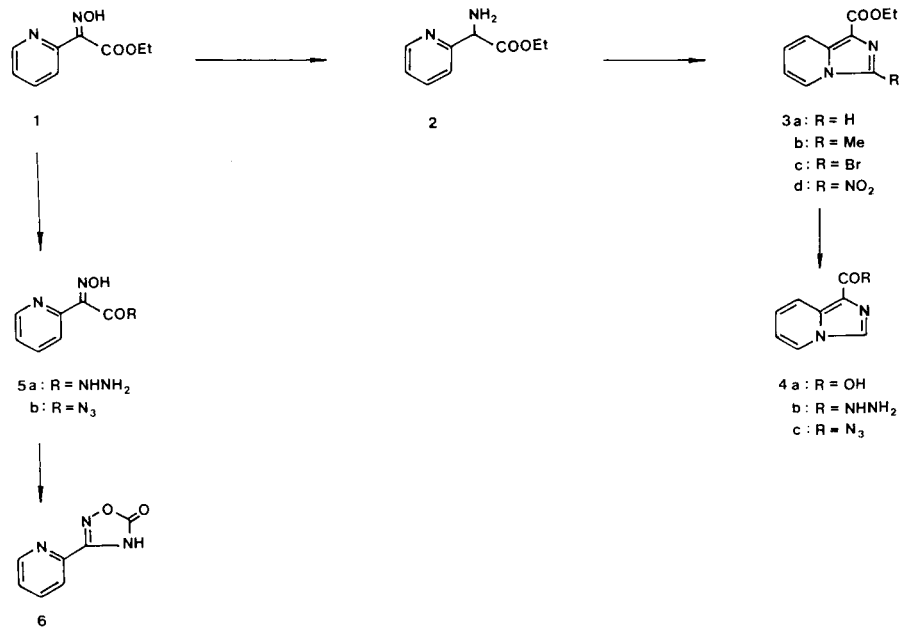
In continuation of our studies on heterocyclic amino acids and syntheses of heterocycles from them [1-7], we would like to report on some new synthetic approaches for imidazo[1,5-*a*]pyridines and imidazo[1,5-*a*]quinolines. Representatives of both systems have been found to possess interesting biological activity [8,9].

From the synthetic point of view there are only few methods leading to these systems. Imidazo[1,5-*a*]pyridines have been synthesized from acylaminoalkylpyridines [10-12] and from 2-benzoylpyridine by the Leuckart reaction [13]. On the other hand, imidazo[1,5-*a*]quinolines can be obtained either by thermolysis of 2-quinolylacetylazide [14] or from quinoline and dilithium TosMIC [15] and as a by-product in a Wittig reaction of an imidazole derivative [16].

We have developed the synthesis of both systems from the corresponding heterocyclic amino acids. It is well known that among nonproteinogenic amino acids those which are substituted with a heterocyclic residue represent an important group and exhibit various biological activities [17-20]. They have also served as starting material for heterocyclic rings [21]. When ethyl 2-(pyridyl-2')glycinate (**2**), prepared from ethyl (pyridyl-2')acetate *via* the hydroxyimino derivative **1**, is treated either with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) or with diethoxymethyl acetate or with triethyl orthoformate in neither case the anticipated amidine or enamine could be isolated. Instead the bicyclic heterocycle **3a** was formed in 31-87% yield, the best yield being obtained with DMF-DMA. In a similar manner with *N,N*-dimethylacetamide dimethyl acetal the 3-methyl analog **3b** could be prepared.

The ester function of **3a** could be hydrolyzed into the



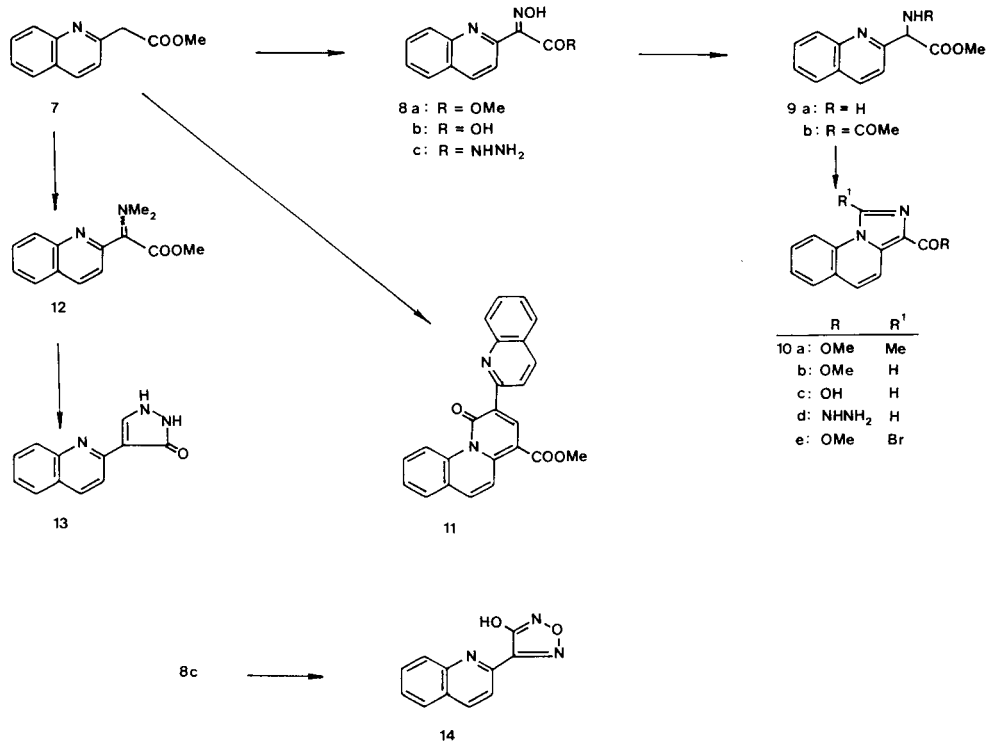
acid **4a** or transformed into the corresponding hydrazide **4b** or azide **4c**. We have tried to thermolyse the later compound by boiling it in chloroform in order to obtain an isocyanate, but after 2 hours the compound was recovered unchanged. Compound **3a** is easily nitrated or brominated to give the 3-substituted derivatives **3c** or **3d**. This is consistent with the observed reactivity of imidazo[1,5-*a*]pyridines for electrophiles since it was found that positions 1 and 3 are attacked [10,22-24]. If, however, a carbanion is generated the reaction proceeds at position 5 [25]. Recently, it was found that the parent compound displays dual reactivity and acylation can occur either at position 1 or 3, depending on reaction conditions [26]. Nitrosation of **3a** was unsuccessful and the starting compound was recovered.

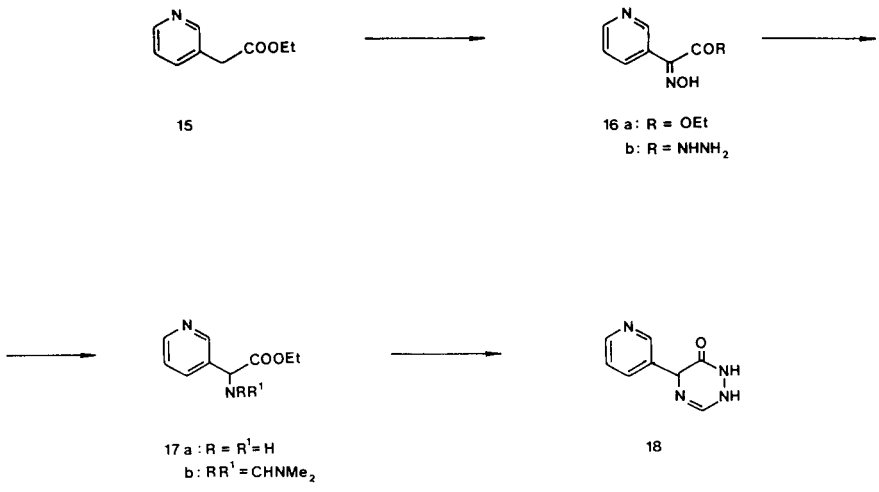
The ester **1** was transformed into the hydrazide **5a** and further into the acylazide **5b** and this thermally rearranges into the corresponding isocyanate which is immediately cyclized into the corresponding 1,2,4-oxadiazolin-5-one derivative **6** [27].

In the quinoline series, the ester **7** is nitrosated to give the oxime **8a** in good yield. Reduction to the amino function was achieved either by catalytic hydrogenation to **9a** or by reductive acetylation by zinc and acetic anhydride to yield **9b**. Compound **9a** was transformed with DMF-DMA or *N,N*-dimethylacetamide dimethyl acetal into the tricyclic system **10b** or **10a** in high yield. In a similar manner as the bicyclic system **3**, compound **10b** was easily brominated to give **10e**. Nitration, however, afforded a mixture of products which we were unable to separate.

The ester **7** when treated with triethyl orthoformate in order to prepare the corresponding ethoxymethylene derivative, gave unexpectedly the benzo[*c*]quinolizin-1-one derivative **11**. Its formation is envisaged as condensation of the *in situ* formed ethoxymethylene derivative with the starting compound **7**. Also under varied reaction conditions only the tricyclic compound **11** could be obtained. Benzo[*c*]quinolizin-1-ones have been obtained previously from 2-vinylpyridine and dimethyl acetylenedicarboxylate [28], from alkylquinolines and malonates, [29], from quinoline 1-oxide and ylidenemalonodinitriles [30], from thiazolo[3,2-*a*]quinolinium hydroxide and fumaronitrile [31] or from quinolyl enamines and acetic anhydride or other anhydrides, ketene or diethyl malonate [31]. If, however, the ester **7** reacted with DMF-DMA, the corresponding enamine **12** was easily obtained in excellent yield. The ethyl ester analogue of **12** has been obtained before from the (quinolyl-2')acetate and the Vilsmeier reagent [32]. The enamine **12** was transformed with hydrazine into the substituted pyrazolinone **13**.

Compound **8c**, prepared similarly as the pyridine analog **5a**, did not give upon nitrosation the anticipated acyl azide and instead the 1,2,5-oxadiazole derivative **14** was obtained at low temperature. It has been postulated [14,27] that the solvent and the kind of heteroaryl group determine whether upon thermolysis an 1,2,5- or an 1,2,4-oxadiazole derivative is formed. Since our synthetic approach differs from the published one, it was of interest to





evaluate the difference in the thermodynamic stability of both systems. A comparison of total energies, calculated by the MMPMI method [33] and assuming the two heterocyclic rings almost coplanar, revealed that for compound **6** the total energy amounts 13.2 kcal/mol and for the unknown pyridyl analog of **14** the corresponding value is 14.3 kcal/mol. On the other hand, the difference between compound **14** (13.7 kcal/mol) and the hypothetical quinolyl analog of **6** (14.2 kcal/mol) is also very small.

The 3-substituted pyridine **17a** could be prepared in a similar manner as described above, from compound **15** *via* **16a**. Here, of course, no cyclization on the ring nitrogen atom can take place. The amino acid **17a** afforded with DMF-DMA the corresponding amidine **17b** and this yielded with hydrazine the pyridyl-triazine **18**. For this compound several tautomeric structures are possible. On hand of its ^{1}H nmr spectrum which showed two doublets for H_3 and H_5 it follows that in solution only compound with the structure **18** is present. For other forms for H_5 a singlet should be observed.

In the 3-pyridyl series the hydrazide **16b** when nitrosated yielded as the sole product 3-cyanopyridine. Its formation can be explained in terms of nitrogen elimination and formation of an intermediate oxazetinone which eliminates carbon dioxide. There is a striking difference in the ease of formation of cyanopyridines. 2-Cyanopyridine is formed from **5b** in 80% yield at room temperature after 3 hours, whereas 3-cyanopyridine is formed so quickly that we were not able to isolate the corresponding precursor, the azide.

The versatility of these transformations for the preparation of other heterocyclic amino acids and heterocyclic systems is in progress.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a JEOL JNM FX-90Q spectrometer or a Varian M 360L spectrometer with TMS as internal standard. Infrared spectra were recorded on a Perkin-Elmer 727B spectrometer and high resolution mass spectra were recorded with an CEC-20-110C instrument. Microanalyses were obtained on a Perkin-Elmer Analyzer 240C.

1-Ethoxycarbonyl-3-methylimidazo[1,5-*a*]pyridine (**3b**).

A solution of dry ethyl 2-(pyridyl-2')glycinate [34] (**2**) (1.50 g, 8.3 mmoles) in dry toluene (4 ml) was treated with *N,N*-dimethylacetamide dimethyl acetal (1.15 g, 8.6 mmoles) and the mixture was heated under reflux 2 hours. The volatile components were evaporated *in vacuo* and the oily residue crystallized overnight. The filtered product was washed with ethyl acetate and hexane and crystallized from heptane to give **3b** (0.72 g, 42% yield), mp 68-70°; ^{1}H nmr (deuteriochloroform): δ 8.00 (m, H_5), 7.65 (m, H_8), 6.96 (m, H_7), 6.68 (m, H_6), 4.39 (q, CH_2CH_3), 2.68 (s, CH_3), 1.45 (t, CH_2CH_3), $J_{5,6}$ = 6.77, $J_{7,8}$ = 9.68, J_{Et} = 6.70 Hz.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.43; H, 6.10; N, 13.64.

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

a) This compound was prepared in essentially the same manner as the above analog, but using DMF-DMA. The product was crystallized from ethyl acetate, mp 140-142° (87% yield); ^{1}H nmr (deuteriochloroform): δ 8.20 (m, H_5), 8.06 (s, H_3), 8.00 (m, H_8), 7.11 (ddd, H_7), 6.72 (ddd, H_6), 4.43 (q, CH_2CH_3), 1.44 (t, CH_2CH_3), $J_{5,6}$ = $J_{6,7}$ = 6.88, $J_{6,8}$ = $J_{5,7}$ = 1.0, $J_{7,8}$ = 9.83, J_{Et} = 6.90 Hz.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.48; H, 5.62; N, 14.83.

b) The same compound was obtained in 77% yield when diethoxymethyl acetate was used and the reaction time was 30 minutes. With triethyl orthoformate the compound was obtained in 31% yield after 1.5 hours of reaction time.

Imidazo[1,5-*a*]pyridine-1-carboxylic Acid (**4a**).

A solution of **3a** (0.72 g, 3.8 mmoles) in ethanol (15 ml of 96%) was treated with aqueous sodium hydroxide (0.17 g in 5 ml) and the mixture was heated under reflux for 1 hour. The cooled solution was neutralized with glacial acetic acid and the separated product was filtered and washed with water, 5% aqueous sodium bicarbonate and ethanol. The product was crystallized from aqueous ethanol to give **4a**, mp 220-221° (0.47 g, 69% yield).

Anal. Calcd. for $C_8H_6N_2O_2 \cdot H_2O$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.31; H, 4.24; N, 15.34.

Imidazo[1,5-*a*]pyridine-1-carboxylic Acid Hydrazide (**4b**).

The ester **3a** (0.4 g, 2.1 mmoles) was suspended in absolute ethanol (1 ml), hydrazine hydrate (4 ml of 95%) was added and the reaction mixture was heated under reflux for 2.5 hours. The solvent was evaporated *in vacuo* and the obtained colourless product was crystallized from ethanol (0.35 g, 95%), mp 180-182°; ^{1}H nmr (DMSO-d_6): δ 8.73 (broad s, CONHNH$_2$), 8.13 (m, H_5), 8.07 (s, H_3), 7.72 (m, H_8), 6.74 (m, H_7), 6.55 (m, H_6), 4.21 (broad s, NHNH_2), $J_{7,8}$ = 9.29 Hz.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.21; H, 4.66; N, 31.58.

Imidazo[1,5-*a*]pyridine-1-carboxylic Acid Azide (**4c**).

The azide was prepared from **4b** by nitrosation in the usual manner in 85% yield, mp 142-146° dec; ir spectrum: 2150 cm^{-1} (N_3).

3-Bromo-1-ethoxycarbonylimidazo[1,5-*a*]pyridine (**3c**).

Compound **3a** (0.48 g, 2.5 mmoles) was dissolved in glacial acetic acid (5 ml) and at room temperature a solution of bromine (0.4 g, 2.5 mmoles) in glacial acetic acid (2 ml) was added dropwise under stirring. After the addition was complete, stirring was continued for 5 minutes, the product was filtered and crystallized from water (0.40 g, 59% yield), mp 115-117°; ^{1}H nmr (DMSO-d_6): δ 8.33 (ddd, H_5), 8.05 (ddd, H_8), 7.38 (ddd, H_7), 7.11 (ddd, H_6), 4.34 (q, CH_2CH$_3$), 1.36 (t, CH$_2$CH_3), $J_{5,6}$ = 6.93, $J_{5,7}$ = $J_{5,8}$ = 1.26, $J_{6,7}$ = 6.66, $J_{6,8}$ = 1.35, $J_{7,8}$ = 9.09, J_{Et} = 7.11 Hz.

Anal. Calcd. for $C_{10}H_9BrN_2O_2$: C, 44.63; H, 3.37; N, 10.41. Found: C, 44.33; H, 3.38; N, 10.47.

1-Ethoxycarbonyl-3-nitroimidazo[1,5-*a*]pyridine (**3d**).

Compound **3a** (190 mg, 1.0 mmole) was dissolved in glacial acetic acid (10 ml) and the solution was heated to 70-80°. Under stirring a mixture of nitric acid (100 mg of 64%), sulfuric acid (150 mg of 96%) and glacial acetic acid (1 ml) was added dropwise. The reaction mixture turned first green and after a few minutes red. After the red color had developed the solution was chilled on ice to 0°, diethyl ether (20 ml) was added. The ethereal layer was evaporated *in vacuo* to dryness and the oily residue was treated with some ethanol. The solid material was crystallized from ethyl acetate (30 mg, 13%), mp 181-184° (pale yellow crystals).

Anal. Calcd. for $C_{10}H_9N_3O_4$: C, 51.06; H, 3.86; N, 17.87. Found: C, 50.69; H, 3.86; N, 17.72.

2-Hydroxyimino(pyridyl-2′)glyoxylic Acid Hydrazine (**5a**).

A solution of the ester **1** (1.94 g, 10 mmoles) in ethanol (20 ml) was treated with hydrazine hydrate (1.0 g of 95%) and the mixture was heated under reflux for 1.5 hours. After the solvent was evaporated *in vacuo* the product was crystallized from ethanol (1.3 g, 72%), mp 165-168°; ^{1}H nmr (DMSO-d_6): δ 11.82 (broad s, =NOH), 9.23 (s, CONHNH$_2$), 8.40 (m, $H_{6'}$), 7.76-7.38 (m, $H_{3''}$ and $H_{4'}$), 7.19 (m, $H_{5'}$), 4.28 (broad s, CONHNH$_2$), $J_{5',6'}$ = 5.75 Hz.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.47; N, 31.10. Found: C, 46.79; H, 4.50; N, 31.05.

2-Hydroxyimino(pyridyl-2′)glyoxylic Acid Azide Hydrochloride (**5b**).

The above hydrazide **5a** (2.0 g, 11.1 mmoles) was dissolved in hydrochloric acid (12 ml of 10%), the solution was cooled to 0° and under stirring an aqueous solution of sodium nitrite (0.77 g, 11.1 mmoles, in 2 ml) was added portionwise. Stirring was continued for 30 minutes and the product was filtered, washed with diethyl ether and ethanol (0.76 g, 30% yield), mp 210-212° dec.

Anal. Calcd. for $C_7H_6ClN_5O_2$: C, 36.93; H, 2.65; N, 30.76. Found: C, 36.79; H, 2.75; N, 30.56.

3-(Pyridyl-2′)-1,2,4-oxadiazolin-5-one (**6**).

To an ice-cold solution of the hydrazide **5a** (0.96 g, 5.3 mmoles) in hydrochloric acid (10 ml of 10%) was treated under stirring with a solution of aqueous sodium nitrite (0.38 g, 5.5 mmoles, in 1 ml). Thereafter water (5 ml) was added and the mixture was neutralized with sodium carbonate. Water (10 ml) was added, the solution was extracted with chloroform (4 times with 10 ml portions), dried and heated under reflux for 75 minutes. Upon evaporation of the solvent the residue was crystallized from a mixture of benzene and ethanol (0.22 g, 25% yield), mp 197-199° (lit [27] gives mp 199-200°).

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.54; H, 3.09; N, 25.76. Found: C, 51.82; H, 3.08; N, 25.94.

Methyl 2-Hydroxyimino-3-(quinolyl-2′)glyoxylate (**8a**).

To a solution of methyl (quinolyl-2′)acetate (**7**) (5.03 g, 25 mmoles) in glacial acetic acid (15 ml) a solution of sodium nitrite (1.75 g, 25.4 mmoles) in water (5 ml) was added dropwise under stirring at 10-15°. Stirring was continued at room temperature for 20 minutes, water (25 ml) was added and the mixture was stirred for 1 hour. The separated product was filtered, washed with water and aqueous 5% sodium hydrogen carbonate. The solid was crystallized from benzene (4.37 g, 76% yield), mp 152-154° (lit [14] gives mp 153-154°).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.95; H, 4.46; N, 12.30.

2-Hydroxyimino-3-(quinolyl-2′)glyoxylic Acid (**8b**).

The above ester **8a** (0.46 g, 2 mmoles) and aqueous potassium hydroxide (5 ml of 10%) were stirred at room temperature for 2 hours. The mixture was acidified with hydrochloric acid (1:1) to *p*H 3-4, the separated product was filtered and washed with water (0.23 g, 53% yield), mp 175-177°.

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.31; H, 3.74; N, 12.65.

2-Hydroxyimino(quinolyl-2′)glyoxylic Acid Hydrazide (**8c**).

The compound was prepared in a similar manner as the pyridyl analog **5a** after 2.5 hours in 87% yield. The product was crystallized from methanol, mp 177-180°; ^{1}H nmr (DMSO-d_6): δ 11.45 (broad s, NOH), 9.05 (broad s, CONHNH$_2$), 8.14-7.21 (m, Het), 4.34 (broad s, CONHNH_2).

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.38; H, 4.38; N, 24.34. Found: C, 57.24; H, 4.45; N, 23.93.

Methyl 2-(Quinolyl-2′)glycinate (**9a**).

Compound **8a** (3.5 g, 15.2 mmoles) was dissolved in methanol (50 ml), palladized carbon (0.2 g of 10%) was added and the mixture was hydrogenated in a Parr hydrogenation apparatus at 3.1-3.5 bar for 6 hours. Upon filtration and evaporation the solvent *in vacuo* a brownish red oily product (3.10 g, 94% yield) was obtained. The product was used for further transformations without purification.

The compound was characterized after its transformation into

the hydrazide with methanolic hydrazine hydrate (93% yield), mp 114-117° (orange crystals from methanol); ^{1}H nmr (DMSO-d_6): δ 9.21 (broad s, CONHNH_2), 8.37-7.55 (m, 6H, Het), 4.68 (s, CH), 3.55 (broad s, two NH_2).

Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.03; H, 5.62; N, 25.86.

Methyl *N*-Acetyl-2-(quinolyl-2')glycinate (**9b**).

To a mixture of compound **8a** (0.23 g, 1 mmole), acetic anhydride (1 ml) and glacial acetic acid (3 ml) under stirring zinc powder (0.3 g) was added portionwise and temperature was maintained below 30°. Stirring was continued for 1 hour, the reaction mixture was diluted with ice-cold water (20 ml) and stirred for further 30 minutes. It was then extracted with chloroform (3 times with 20 ml), the combined extracts were washed with aqueous sodium bicarbonate (5%), water and dried. The solvent was evaporated to give a pale yellow oil which gradually solidified and was crystallized from a mixture of ethyl acetate and hexane (0.1 g, 43% yield), mp 109-113°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.05; H, 5.63; N, 10.68.

1-Methyl-3-methoxycarbonylimidazo[1,5-*a*]quinoline (**10a**).

A mixture of the glycinate **9a** (0.73 g, 3.4 mmoles), toluene (10 ml) and *N*,*N*-dimethylacetamide dimethyl acetal (0.47 g, 3.5 mmoles) was heated under reflux for 1.5 hour. After the solvent was evaporated *in vacuo* the separated residue was crystallized from ethyl acetate (0.77 g, 95%), mp 166-167°; ^{1}H nmr (deuteriochloroform): δ 8.18-6.94 (m, 6H, Het), 3.82 (s, COOCH_3), 3.05 (s, CH_3).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.57; H, 5.19; N, 11.69.

3-Methoxycarbonylimidazo[1,5-*a*]quinoline (**10b**).

a) A solution of compound **9a** (3.0 g, 13.8 mmoles) in toluene (20 ml) was treated with DMF-DMA (1.7 g, 14.3 mmoles) and the reaction mixture was heated under reflux for 1 hour. After evaporation of the solvent the remaining red pro' -t was crystallized from toluene (2.52 g, 81% yield), mp 159-161°; ^{1}H nmr (DMSO-d_6): δ 8.92 (s, H_1), 8.22 (m, H_9), 7.84-7.17 (m, 5H, Het), 3.71 (s, $COOCH_3$), $J_{8,9}$ = 8.57 Hz.

Anal. Calcd. for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.61; H, 4.53; N, 12.28.

b) Instead of the acetal as under a) diethoxymethyl acetate was used and 0.34 g (94%) of the product, identical as described under a) was obtained.

c) With triethyl orthoformate in excess and after 4 hours under reflux the compound was obtained in 81% yield, again identical with the product as described under a).

Imidazo[1,5-*a*]quinoline-3-carboxylic Acid (**10c**).

The ester **10b** (0.42 g, 1.9 mmoles) was dissolved in methanol (12 ml) and an aqueous solution of potassium hydroxide (0.11 g in 2 ml) was added. The reaction mixture was heated under reflux for 1 hour, chilled and neutralized with glacial acetic acid. The mixture was evaporated to half of its original volume *in vacuo*, water (10 ml) was added and the separated product was washed with water and methanol. The reddish product was crystallized from methanol (0.35 g, 89% yield), mp 272-276° dec.

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.90; H, 3.84; N, 12.80.

The corresponding hydrazide **10d** was prepared from the ester in the usual manner in 89% yield, mp 245-248° (from ethanol).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.43; H, 4.43; N, 24.49.

1-Bromo-3-methoxycarbonylimidazo[1,5-*a*]quinoline (**10e**).

A suspension of the ester **10b** (0.23 g, 1.0 mmole) in glacial acetic acid (15 ml) was treated under stirring portionwise with a solution of bromine (0.16 g, 1.0 mmole) in glacial acetic acid (5 ml). Already during the addition a yellow product separated which was filtered upon completion of the reaction. After crystallization from aqueous ethanol (0.20 g, 64% yield) the product had mp 134-135°; ^{1}H nmr (DMSO-d_6): δ 9.23 (m, H_9), 8.00-7.55 (m, 5H, Het), 2.53 (s, COOCH_3), $J_{8,9}$ = 8.64 Hz.

Anal. Calcd. for $C_{13}H_9BrN_2O_2$: C, 51.17; H, 2.97; N, 9.18. Found: C, 51.18; H, 2.97; N, 9.20.

4-Carbomethoxy-2-(quinolyl-2')benzo[*c*]quinolizin-1-one (**11**).

A mixture of compound **7** (2.01 g, 1.0 mmole), triethyl orthoformate (6 ml) and acetic anhydride (2 ml) was heated under reflux for 2 hours. Upon cooling the separated crystals were filtered and washed with hexane. The product was crystallized from benzene or benzene and hexane (1.0 g, 53% yield), mp 197-198°; high resolution ms: m/e = 380.1170 (M^+); Calcd: 380.1160.

Anal. Calcd. for $C_{24}H_{16}N_2O_3$: C, 75.78; H, 4.24; N, 7.37. Found: C, 75.99; H, 4.65; N, 7.73.

Methyl 2-(Dimethylaminomethylene)-2-(quinolyl-2')acetate (**12**).

A mixture of the ester **7** (3.18 g, 1.58 mmoles), DMF-DMA (5 ml) and toluene (15 ml) was heated under reflux for 2 hours. The solvent was evaporated *in vacuo* and the solid residue was crystallized from a mixture of benzene and hexane or heptane (3.6 g, 89% yield), mp 121-123°.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 69.98; H, 6.31; N, 10.55.

4-(Quinolyl-2')pyrazolin-3(2*H*)-one (**13**).

The above compound **12** (0.257 g, 1.0 mmole), methanol (10 ml) and hydrazine hydrate (0.1 ml of 95%) were heated under reflux for 30 minutes. Upon evaporation of the solvent the product was crystallized from methanol (0.17 g, 80% yield), mp 274-275°.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.44; H, 4.45; N, 19.75.

3-Hydroxy-4-(quinolyl-2')-1,2,5-oxadiazole (**14**).

To an ice-cold solution of the hydrazide **8c** (0.6 g, 2.6 mmoles) in hydrochloric acid (6 ml of 10%) an aqueous solution of sodium nitrite (0.18 g, 2.6 mmoles, in 0.5 ml) was added under stirring. The separated product was filtered, washed with water and crystallized from benzene and subsequently from ethanol (0.54 g, 97%), mp 172-174° (lit [14] gives mp 174-174.5°).

Anal. Calcd. for $C_{11}H_7N_3O_2$: C, 61.97; H, 3.31; N, 19.72. Found: C, 61.71; H, 3.24; N, 19.68.

Ethyl (Pyridyl-3')glyoxylate-2-oxime (**16a**).

To an ethanolic solution of sodium ethylate, prepared from sodium (1.4 g) and absolute ethanol (20 ml), anhydrous diethyl ether (100 ml) was added, the mixture was cooled to 0° and under stirring ethyl 3-pyridylacetate (10.0 g, 60.5 mmoles) was added. Stirring was continued and isoamyl nitrite (7.0 g, 60.0 mmoles) was added portionwise by maintaining temperature of the reac-

tion mixture 5-10°. After addition was complete stirring was continued for 1 hour, water (30 ml) was added and the mixture was acidified with glacial acetic acid. After stirring for 1 hour the product was filtered, washed with ethanol and dried. After crystallization from ethanol (2.0 g, 17%) the product had mp 166-171°; ^{1}H nmr (*N,N*-dimethylformamide-d_7): δ 8.70 (m, H_2 and H_6), 8.00 (m, H_4), 7.50 (dd, H_5), 4.40 (q, CH_2CH_3), 3.60 (broad s, NO*H*), 1.30 (t, CH_2CH_3), $J_{4,5}$ = 9.71, $J_{5,6}$ = 5.39 Hz).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.42. Found: C, 56.09; H, 5.41; N, 14.22.

2-Hydroxyimino(pyridyl-3')glyoxylic Acid Hydrazide (**16b**).

The compound was prepared in a similar manner as the pyridyl analog **5a** in 95% yield, mp 229-232° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 11.55 (broad s, NOH), 9.21 (broad s, CONHNH_2), 8.39 (dd, $H_{2'}$), 8.19 (ddd, $H_{6'}$), 7.63 (ddd, $H_{4'}$), 7.02 (ddd, $H_{5'}$), 4.34 (broad s, CONHNH_2), $J_{2',4'}$ = 2.09, $J_{2',5'}$ = 1.14, $J_{4',5'}$ = 7.97, $J_{4',6'}$ = 1.71, $J_{5',6'}$ = 4.56 Hz.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 47.01; H, 4.44; N, 30.88.

Ethyl 2-(Pyridyl-3')glycinate (**17**).

To a solution of compound **16a** (1.5 g, 7.7 mmoles) is absolute ethanol (120 ml) palladiazed carbon (0.2 g of 10%) was added and the mixture was hydrogenated at 3.0-3.5 bar for 3 hours in a Parr hydrogenation apparatus. The catalyst was filtered and the solvent evaporated *in vacuo* to give the pale yellow oil (0.89 g, 64%); ^{1}H nmr (deuteriochloroform): δ 8.60 (m, H_2 and H_6), 7.70 (m, H_1), 7.30 (dd, H_3), 4.60 (s, C*H*), 4.10 (q, CH_2CH_3), 2.10 (broad s, NH_2), 1.10 (t, CH_2CH_3), $J_{4,5}$ = 9.51, $J_{5,6}$ = 5.49 Hz.

With *N,N*-dimethylformamide dimethyl acetal in boiling toluene the compound was transformed into its *N,N*-dimethylaminomethylene derivative **17b** (55% yield) as an oil; ^{1}H nmr (deuteriochloroform): δ 8.60 (m, H_2 and H_6), 7.90 (m, H_4), 7.50 (s, -CH=N), 7.30 (dd, H_5), 5.0 (s, -CH-N=), 4.20 (q, CH_2CH_3), 2.90 (s, two Me), $J_{4,5}$ = 9.64, $J_{5,6}$ = 5.36 Hz.

5-(Pyridyl-3')-4,5-dihydro-1,2,4-triazin-6(1*H*)-one (**18**).

A mixture of the compound **17b** (1.12 g, 4.8 mmoles), ethanol (12 ml) and hydrazine hydrate (0.45 g of 95%) was heated under reflux for 2 hours. After evaporation of the solvent *in vacuo* the pale yellow solid was filtered and washed with benzene. It was crystallized from a mixture of benzene and ethanol (0.52 g, 61% yield), mp 187-190°; ^{1}H nmr (DMSO-d_6): δ 10.25 (broad s, H_1), 8.56-8.49 (m, $H_{2'}$ and $H_{6'}$), 7.74 (ddd, $H_{4'}$), 7.65 (broad s, H_4), 7.40 (ddd, $H_{5'}$), 7.05 (s, H_3), 5.05 (d, H_5), $J_{3,4}$ = 3.87, $J_{4,5}$ = 1.44, $J_{2',4'}$ = $J_{4',6'}$ = 1.96, $J_{2',5'}$ = 0.61. $J_{4',5'}$ = 7.85, $J_{5',6'}$ = 5.05 Hz.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.45; H, 4.59; N, 31.40.

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