The Synthesis of 3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)methyl]imidazo[1,2-*x*]azines and Related Compounds, Intermediates in the Formation of Azaaplysinopsin Derivatives

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Dedicated to Professor Gottfried Heinisch, Leopold-Franzens-Universität, Innsbruck, on the occasion of his 60th birthday

4-(2-Bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**) reacts with *N,N*-dimethyl-*N'*-heteroarylformamidines **7** to form imidazoazine derivatives **9** with the oxazolone ring connected through a conjugated double bond to the fused imidazole system at position 3. Compounds **9** were transformed with sodium methoxide in methanol into 2-benzoylamino-3-dimethylamino-3-imidazoazinylpropenoates **10**, while by treatment with hydrochloric acid in methanol, 3-(benzoylaminoacetyl)imidazoazines **12** were formed. The synthesis of compounds **9** represents a facile route to intermediates in the synthesis of azaaplysinopsin and related systems.

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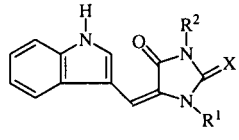
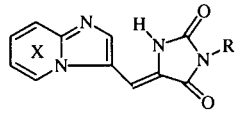
Aplysinopsins **1**, isolated from the sponge *Aplysinopsis reticulata* [1] has been shown to be active as a specific cytotoxin of cancer cells [2] and to affect neurotransmission [3]. The classical approach to the synthesis of C-5 unsaturated hydantoins, is based on the coupling of an aromatic aldehyde and an appropriately substituted hydantoin [4,5]. Another reaction is tandem Staudinger/aza-Wittig reaction followed by electrocyclic ring closure [6]. This methodology allows the formation of nitrogen containing heterocycles resulting in the synthesis of several aplysinopsin-type alkaloids [7].

Since imidazo[1,2-*a*]azine derivatives are an interesting class of heterocyclic compounds, as for example, imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine skeletons are basic structures of natural alkaloids, such as alchorneine [8], in the Y base as a component of $tRNA^{Phe}$ [9,10] and new acyclovir analogs exhibit an antiherpetic activity on HIV-1,2 [11], recently considerable interest arose in the synthesis of azaaplysynopsin analogs. Aza-Wittig-type reactions of iminophosphorans have been used to construct azacarboline and azaaplysinopsin type alkaloids by electrocyclic ring closure [12]. Recently, annulation of carbodiimides on solid support alumina selectively gives (*Z*)-hydantoins **2** [13] (Scheme 1). The method is represented by condensation of 3-formylimidazo[1,2-*a*]azines with ethyl azidoacetate in the presence of sodium ethoxide giving substituted oxazole intermediates, followed by transformation with triphenylphosphine into the corresponding iminophosphorane derivatives. An aza-Wittig type reaction with aliphatic or aromatic isocyanates gives carbodiimides which give upon heating azaaplysinopsin derivatives [13].

Scheme 1



1, X = NH; $R^1 = R^2 = CH_3$
X = O; $R^1 = R^2 = H$

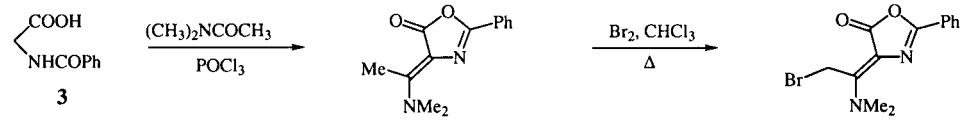


2, X = CH, N
R = Et, Ph

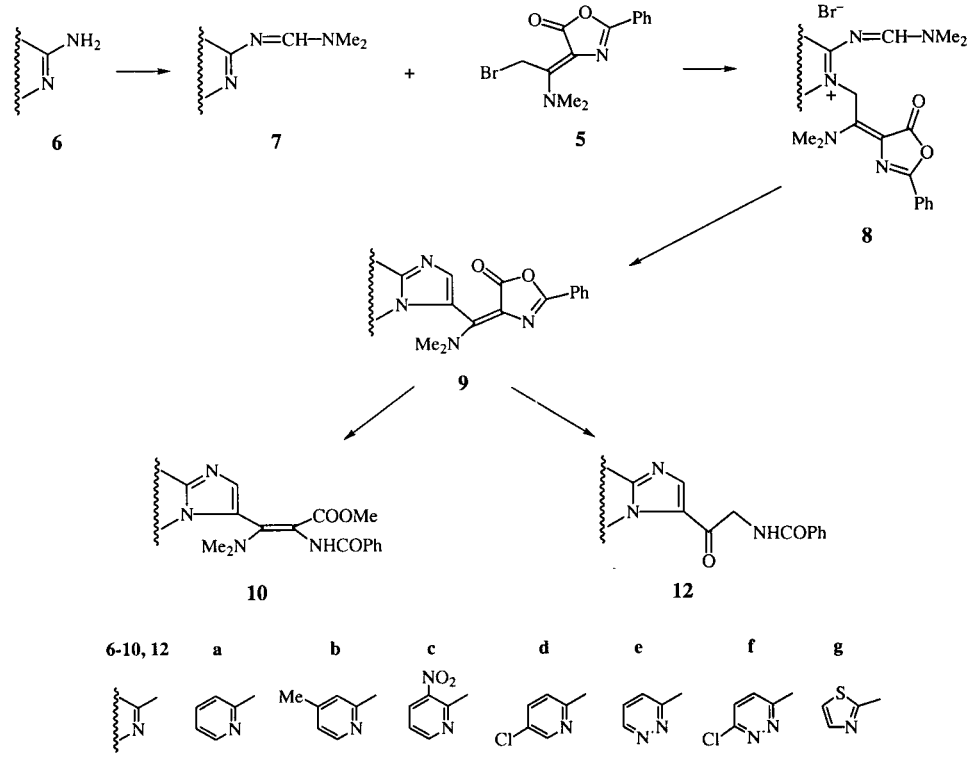
In continuation of our studies in the synthesis of β-heteroaryl-α,β-dehydroamino acids and their derivatives, we extended the method, described previously, in which *N,N*-dimethyl-*N'*-heteroarylformamidine is treated with an α-halo ketone to give a fused imidazole system [14,15]. Namely, when we used 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**) instead of an α-halo ketone fused imidazole with oxazolone ring connected through a conjugated double bond to imidazole system can be formed in one step.

4-(2-Bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**) was prepared in two steps from hippuric acid (**3**) and *N,N*-dimethylacetamide in the presence of phosphorus oxychloride to give 4-(1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**4**) as an intermediate, followed by treatment with bromine in boiling chloroform, in 55% overall yield (Scheme 2).

Scheme 2



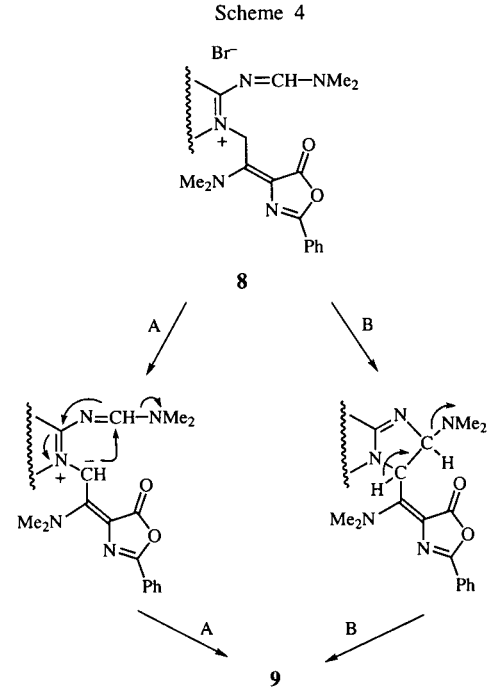
Scheme 3



The following heterocyclic formamidines containing an α-nitrogen atom in the cyclic system, prepared from heterocyclic amines **6** and *N,N*-dimethylformamide dimethyl acetal according to the procedures described in the literature, were used in this study. These compounds are *N,N*-dimethylamino-*N'*-(2-pyridinyl)formamidine (**7a**) [16], *N,N*-dimethylamino-*N'*-(4-methyl-2-pyridinyl)formamidine (**7b**) [16], *N,N*-dimethylamino-*N'*-(3-nitro-2-pyridinyl)formamidine (**7c**) [16], *N,N*-dimethylamino-*N'*-(5-chloro-2-pyridinyl)formamidine (**7d**) [16], *N,N*-dimethylamino-*N'*-(3-pyridazinyl)formamidine (**7e**) [16], *N,N*-dimethylamino-*N'*-(6-chloro-3-pyridazinyl)formamidine (**7f**) [16] and *N,N*-dimethylamino-*N'*-(2-thiazolyl)formamidine (**7g**) [15]. These were treated with 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**) in acetonitrile or *N,N*-dimethylformamide. When a mixture of both components was allowed to stand in dimethylformamide at room temperature for 12 hours the quaternary salts were formed, which were cyclized into fused imidazoazoles and imidazoazines **9** by heating (Scheme 3). The quaternary salts were usually not isolated, except in the reaction of 3-amino-6-chloropyridazine (**6f**) when 1-(2-dimethylamino-2-(2-phenyl-5-oxo-2-oxazolin-4-ylidene)-ethyl-6-dimethylaminomethyleneamino-3-chloropyridazinium bromide (**8f**) was isolated and identified.

Cyclization can be explained by two possible reaction pathways. In pathway **A,** substitution of the dimethylamino group in the formamidine moiety occurs by an anion formed from the active methylene group, followed by elimination of a proton to give the cyclized product. In pathway **B,** addition of the anion formed from the active

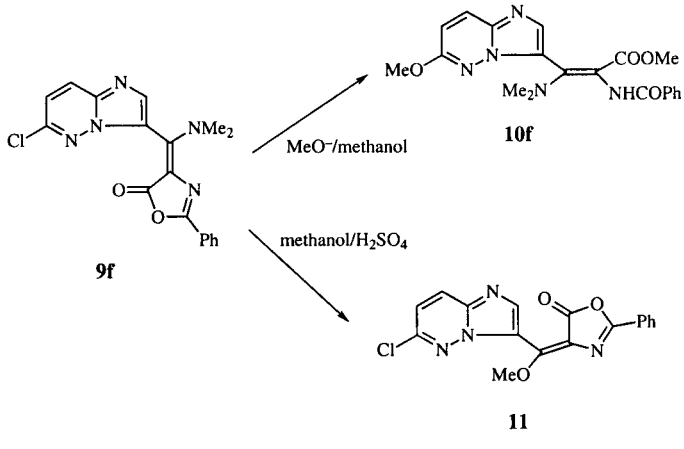
Scheme 4



methylene group takes place across the C=N double bond of the formamidine part of the molecule followed by elimination of the dimethylamino group of the former formamidine moiety. (Scheme 4). This second pathway seems more plausible since some additional products have been isolated [17]. In this manner compounds **9a-9g** were prepared.

Products **9** were treated with sodium methoxide in methanol to give methyl 2-benzoylamino-3-dimethylamino-3-heteroarylpropenoates **10** in 70-95% yield. In the case of the 6-chloroimidazo[1,2-*b*]pyridazine derivative **9f,** substitution of chlorine occurred to give the corresponding 6-methoxyimidazo[1,2-*b*]pyridazine derivative **10f** in 82% yield. On the other hand, when the same compound was treated with methanol in the presence of concentrated sulfuric acid, substitution of the dimethylamino group attached to the double bond took place to give 3-[(2-phenyl-5-oxo-2-oxazolin-4-ilidene)(methoxy)-methyl]-6-chloroimidazo[1,2-*b*]pyridazine (**11**) in 45% yield (Scheme 5). When 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolin-4-ylidene)methyl]imidazo[1,2-*a*]pyridine (**9a**) was heated with a mixture of methanol and concentrated hydrochloric acid (1:1), hydrolysis followed by decarboxylation occurred to give 3-(benzoylaminoacetyl)-imidazo[1,2-*a*]pyridine (**12a**). Similarly, compounds **12b-g** were prepared (Scheme 3).

Scheme 5



Since, this method represents a facile route to compounds **9**, intermediates in the synthesis of azaaplysinopsins and related systems, further research is under way.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian E-360 (60 MHz) and on a Bruker Avance DPX 300 (300 MHz) spectrometer in such solvent as dimethyl-d_6 sulfoxide, deuteriochloroform or deuteriotrifluoroacetic acid with tetramethylsilane as the internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. Mass spectra were obtained on an Autospeck Q spectrometer .

The following formamidines were prepared from heterocyclic amines **6** and *N,N*-dimethylformamide dimethyl acetal by procedures described in the literature: *N,N*-dimethylamino-*N'*-(2-pyridinyl)formamidine (**7a**) [16], *N,N*-dimethylamino-*N'*-(4-methyl-2-pyridinyl)formamidine (**7b**) [16], *N,N*-dimethylamino-*N'*-(3-nitro-2-pyridinyl)formamidine (**7c**) [16], *N,N*-dimethylamino-*N'*-(5-chloro-2-pyridinyl)formamidine (**7d**) [16], *N,N*-dimethylamino-*N'*-(3-pyridazinyl)formamidine (**7e**) [16], *N,N*-dimethylamino-*N'*-(6-chloro-3-pyridazinyl)formamidine (**7f**) [16] and *N,N*-dimethylamino-*N'*-(2-thiazolyl)formamidine (**7g**) [15].

4-(2-Bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**).

To a mixture of hippuric acid (**3**, 53.76 g, 0.3 mole) and phosphorus oxychloride (70 ml, 0.75 mole) stirred in an ice bath, *N,N*-dimethylacetamide (70 ml, 0.75 mole) was added dropwise. The mixture was then stirred at 40-45° for 2 hours. The volatile components were evaporated *in vacuo* and the oily residue was poured into crushed ice (200 g). Product **4** was collected by filtration, washed with cold water and dried at room temperature. The dried product was dissolved in chloroform (250 ml) and heated to the boiling point. Bromine (0.35 mole) in chloroform (200 ml) was added and the mixture was heated under reflux for 1.5 hours. The solvent was evaporated *in vacuo* and ethanol (150 ml) was added. The precipitate was collected by filtration and recrystallized from ethanol to give **5** in 55% yield, mp 164-166°; ^{1}H nmr (deuteriochloroform, 300 MHz): δ 3.54 (6H, br s, $N(CH_3)_2$), 4.94 (2H, br s, CH_2), 7.41-7.44 (3H, m, Ph), 7.92-7.96 (2H, m, Ph).

Anal. Calcd. for $C_{13}H_{13}BrN_2O_2$: C, 50.50; H, 4.24; N, 9.06. Found: C, 50.66; H, 4.19; N, 8.91.

1-(2-Dimethylamino-2-(2-phenyl-5-oxo-2-oxazolin-4-ylidene)-ethyl-6-dimethylaminomethyleneamino-3-chloropyridazinium Bromide (**8f**).

A mixture of *N,N*-dimethyl-*N'*-(6-chloro-3-pyridazinyl)formamidine (**7f**, 0.185 g, 0.001 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(*4H*)-oxazolone (**5**, 0.309 g, 0.001 mole) in acetonitrile (2 ml) was heated under reflux for 45 minutes. After cooling, the product was collected by filtration and recrystallized from methanol to give **8f** in 66% yield, mp 187-190°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 3.20-3.41 (m, $N(CH_3)_2$ and H_2O), 6.01 and 6.09 (2H, 2 s, CH_2), 7.40-7.63 (3H, m, Ph), 7.72-7.98 (2H, m, Ph), 8.23 (1H, d, H_4), 8.48 (1H, d, H_5), 9.04 (1H, s, *CH*=N), J_{H4H5} = 9.6 Hz.

Anal. Calcd. for $C_{20}H_{22}BrClN_6O_2 \cdot H_2O$: C, 46.94; H, 4.72; N, 16.42. Found: C, 47.04; H, 4.59; N, 16.13.

3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)methyl]imidazo[1,2-*a*]pyridine (**9a**).

A mixture of 2-aminopyridine (**6a**, 0.659 g, 0.007 mole) and *N,N*-dimethylformamidine dimethyl acetal (1.5 ml, 0.01 mole) was heated under reflux for 2 hours. The solvent was evaporated *in vacuo*. Water (5 ml) was added to the residue and extracted with chloroform (3 times, 8 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in*

vacuo. To the residue 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 1.855 g, 0.006 mole) and acetonitrile (8 ml) were added and the mixture was heated under reflux for 4 hours. After cooling, the product was collected by filtration and recrystallized from methanol to give **9a** in 69% yield, mp 191-193°; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 3.36 and 3.41 (6H, 2 s, $N(CH_3)_2$), 6.89 (1H, ddd, H_6), 7.15-8.15 (9H, m, Ph, H_2, H_5, H_7, H_8), $J_{H5H6} = J_{H6H7} = 6.9$ Hz, $J_{H6H8} = 1$ Hz.

Anal. Calcd. for $C_{19}H_{16}N_4O_2$: C, 68.66; H, 4.85; N, 16.86. Found: C, 68.47; H, 4.67; N, 16.82.

3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)-methyl]-7-methylimidazo[1,2-*a*]pyridine (**9b**).

A mixture of *N,N*-dimethyl-*N'*-(4-methyl-2-pyridyl)formamidine (**7b**, 0.491 g, 0.003 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 0.93 g, 0.003 mole) in acetonitrile (3 ml) was heated under reflux for 1.5 hours. After cooling, the product was collected by filtration and recrystallized from acetonitrile to give **9b** in 57% yield, mp 179-183°; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 2.43 (3H, s, CH_3), 3.33 and 3.39 (6H, 2 s, $N(CH_3)_2$), 6.73 (1H, br d, H_6), 7.25-8.10 (8H, m, Ph, H_2, H_5, H_8), $J_{H5H6} = 7.7$ Hz.

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.17. Found: C, 69.41; H, 5.00; N, 16.34.

3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)-methyl]-8-nitroimidazo[1,2-*a*]pyridine (**9c**).

A mixture of *N,N*-dimethyl-*N'*-(3-nitro-2-pyridyl)formamidine (**7c**, 0.971 g, 0.005 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 1.546 g, 0.005 mole) in acetonitrile (10 ml) was heated under reflux for 7 hours. Half of the solvent was evaporated *in vacuo* and methanol (5 ml) was added. The precipitate was collected by filtration and recrystallized from methanol to give **9c** in 14% yield, mp 248-251°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 3.00 and 3.70 (6H, 2 br s, $N(CH_3)_2$), 7.20 (1H, dd, H_6), 7.49-7.56 (3H, m, Ph), 7.88-7.93 (2H, m, Ph), 8.08 (1H, s, H_2), 8.39 (1H, dd, H_7), 8.67 (1H, dd, H_5), $J_{H5H6} = 6.78$ Hz, $J_{H5H7} = 1.13$ Hz, $J_{H6H7} = 7.7$ Hz.

Anal. Calcd. for $C_{19}H_{15}N_5O_4$: C, 60.47; H, 4.01; N, 18.56. Found: C, 60.54; H, 4.20; N, 18.20.

3-[(Dimethylamino)(2-phenyl-5-oxo-2- oxazolinylidene-4)-methyl]-6-chloroimidazo[1,2-*a*]pyridine (**9d**).

A mixture of *N,N*-dimethyl-*N'*-(5-chloro-2-pyridyl)formamidine (**7d**, 0.917 g, 0.005 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 1.548 g, 0.005 mole) in *N,N*-dimethylformamidine (5 ml) was stirred at room temperature for 24 hours and then heated under reflux for 1 hour. The solvent was evaporated *in vacuo* and water (20 ml) was added. The precipitate was collected by filtration and recrystallized from methanol to give **9d** in 80% yield, mp 174-176°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 3.10 and 3.68 (6H, 2 br s, $N(CH_3)_2$), 7.45 (1H, dd, H_7), 7.50-7.54 (3H, m, Ph), 7.77 (1H, dd, H_8), 7.87-7.92 (2H, m, Ph), 7.90 (1H, s, H_2), 8.47 (1H, dd, H5), $J_{H5H7} = 1.88$ Hz, $J_{H5H8} = 0.75$ Hz, $J_{H7H8} = 9.41$ Hz.

Anal. Calcd. for $C_{19}H_{15}ClN_4O_2$: C, 62.21; H, 4.12; N, 15.27. Found: C, 62.16; H, 4.30; N, 14.97.

3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)-methyl]imidazo[1,2-*b*]pyridazine (**9e**).

A mixture of 2-aminopyridazine (**6e**, 0.950 g, 0.01 mole) and *N,N*-dimethylformamidine dimethyl acetal (1.5 ml, 0.01 mole) in toluene (3 ml) was heated under reflux for 1 hour. The solvent was evaporated *in vacuo*. To the residue 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 1.236 g, 0.004 mole) and *N,N*-dimethylformamidine (4 ml) were added and the mixture was stirred at room temperature for 20 hours and then heated under reflux for 1.5 hours. The solvent was evaporated *in vacuo*. To the oily residue water (20 ml) was added and extracted with chloroform (3 times, 15 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo*. This residue was purified by radial chromatography (Silica gel 60). Fractions containing the product were combined and the eluent (chloroform/methanol 15:1) evaporated *in vacuo* to give **9e** in 25% yield, mp 170-173°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 2.97 and 3.75 (6H, 2 br s, $N(CH_3)_2$), 7.36 (1H, dd, H_7), 7.48-7.55 (3H, m, Ph), 7.85-7.92 (2H, m, Ph), 8.02 (1H, s, H_2), 8.26 (1H, dd, H_8), 8.59 (1H, dd, H_6), $J_{H6H7} = 4.52$ Hz, $J_{H6H8} = 1.51$ Hz, $J_{H7H8} = 9.42$ Hz.

Anal. Calcd. for $C_{18}H_{15}N_5O_2$: C, 64.85; H, 4.54; N, 21.01. Found: C, 64.70; H, 4.70; N, 21.02.

3-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)-methyl]-6-chloroimidazo[1,2-*b*]pyridazine (**9f**).

A mixture of *N,N*-dimethyl-*N'*-(6-chloro-3-pyridazinyl)formamidine (**7f**, 0.554 g, 0.003 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 0.93 g, 0.003 mole) in *N,N*-dimethylformamidine (3 ml) was left at room temperature for 23 hours and then heated under reflux for 45 minutes. The solvent was evaporated *in vacuo* and water (3 ml) and ethanol (6 ml) were added. The precipitate was collected by filtration and recrystallized from a mixture of methanol and chloroform to give **9f** in 81% yield, mp 237-239° (sublimated above 210°); ^{1}H nmr (deuteriotrifluoroacetic acid, 60 MHz): δ 2.78-3.78 (6H, m, $N(CH_3)_2$), 7.05-7.78 (6H, m, Ph, H_7), 8.30 (1H, d, H_8), 8.49 (1H, s, H_2), $J_{H7H8} = 9.5$ Hz.

Anal. Calcd. for $C_{18}H_{14}ClN_5O_2$: C, 58.78; H, 3.84; N, 19.04. Found: C, 58.65; H, 3.54; N, 19.16.

5-[(Dimethylamino)(2-phenyl-5-oxo-2-oxazolinylidene-4)-methyl]imidazo[2,1-*b*]thiazole (**9g**).

A mixture of *N,N*-dimethyl-*N'*-(2-thiazolyl)formamidine (**7g**, 0.465 g, 0.003 mole) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**5**, 0.93 g, 0.003 mole) in *N,N*-dimethylformamidine (3 ml) was allowed to stand at room temperature for 20 hours and then heated under reflux for 5 hours. The solvent was evaporated *in vacuo* and water (5 ml) was added and extracted with chloroform (3 times, 10 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo*. To the residue acetone was added, the precipitate was collected by filtration and recrystallized from acetone to give **9g** in 70% yield, mp 179-181°; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 3.38 (6H, s, $N(CH_3)_2$), 6.89 (1H, br d, H_2), 7.09-8.09 (7H, m, Ph, H_3, H_6), $J_{H2H3} = 4.2$ Hz.

Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.27; H, 3.94; N, 16.74.

Methyl 2-Benzoylamino-3-dimethylamino-3-(imidazo[1,2-*a*]-pyridinyl-3)propenoate (**10a**).

A mixture of sodium methoxide in methanol (0.078 g sodium in 3 ml of methanol) and 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]imidazo[1,2-*a*]pyridine (**9a**, 0.333 g, 0.001 mole) was stirred at room temperature for 19 hours. The solvent was evaporated *in vacuo*. To the residue water (5 ml)

was added and extracted with dichloromethane (3 times, 5 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo*. The residue crystallized from a mixture of diisopropyl ether and methanol and it was recrystallized from a mixture of water and ethanol to give **10a** in 70% yield, mp 194-197°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 2.79 (6H, s, $N(CH_3)_2$), 3.20 (3H, s, OCH_3), 7.07 (1H, dd, H_6), 7.27-7.86 (6H, m, Ph, H_2, H_7, H_8), 7.96-8.23 (2H, m, Ph), 8.59 (1H, br d, H_5), 9.61 (1H, br s, NHCO), $J_{H5H6} = J_{H6H7} = 6.7$ Hz, when deuterium oxide was added the singlet at δ = 9.61 disappeared.

Anal. Calcd. for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.37. Found: C, 65.65; H, 5.48; N, 15.37.

Methyl 2-Benzoylamino-3-dimethylamino-3-(7-methylimidazo[1,2-*a*]pyridinyl-3)propenoate (**10b**).

A mixture of sodium methoxide in methanol (0.053 g sodium in 2 ml of methanol) and 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]-7-methylimidazo[1,2-*a*]pyridine (**9b**, 0.132 g, 0.00038 mole) was allowed to stand at room temperature for 19 hours. The solvent was evaporated *in vacuo*. To the residue water (3 ml) was added and extracted with dichloromethane (3 times, 5 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo*. The oily residue was dissolved in ethanol and water was added until the product percipitated. The percipitate was collected by filtration and recrystallized from ethanol to give **10b** in 95% yield, mp 222-223°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 2.41 (3H, s, CH_3), 2.79 and 2.81 (6H, 2 s, $N(CH_3)_2$), 3.22 and 3.66 (3H, 2 s, $COOCH_3$), 6.89 (1H, dd, H_6), 7.38-7.70 (5H, m, Ph, H_2, H_8), 7.97-8.18 (2H, m, Ph), 8.43 (1H, d, H_5), 9.19 and 9.53 (1H, 2 br s, NHCO), $J_{H5H6} = 6.6$ Hz, $J_{H6H8} = 1.8$ Hz, when deuterium oxide was added the singlets at δ = 9.19 and δ = 9.53 disappeared.

Anal. Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.65; H, 5.86; N, 14.80. Found: C, 66.44; H, 5.88; N, 14.83.

Methyl 2-Benzoylamino-3-dimethylamino-3-(6-chloroimidazo[1,2-*a*]pyridinyl-3)propenoate (**10d**).

A mixture of sodium methoxide in methanol (0.18 g of sodium in 8 ml of methanol) and 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]-6-chloroimidazo[1,2-*a*]pyridine (**9d**, 0.736 g, 0.002 mole) was stirred at room temperature for 5 hours. The solvent was evaporated *in vacuo* and water (10 ml) was added to the residue. The precipitate was collected by filtration and recrystallized from a mixture of water and ethanol to give **10d** in 29% yield, mp 196-199°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 2.78 (6H, s, $N(CH_3)_2$), 3.20 (3H, s, $COOCH_3$), 7.38 (1H, dd, H_7), 7.50-7.62 (3H, m, Ph), 7.71 (1H, dd, H_8), 7.74 (1H, s, H_2), 8.00-8.04 (2H, m, Ph), 8.74 (1H, dd, H_5), 9.51 (1H, br s, NHCO), $J_{H5H7} = 2.26$ Hz, $J_{H5H8} = 0.76$ Hz, $J_{H7H8} = 9.42$ Hz.

Anal. Calcd. for $C_{20}H_{19}ClN_4O_3$: C, 60.23; H, 4.80; N, 14.05. Found: C, 60.03; H, 4.76; N, 13.97.

Methyl 2-Benzoylamino-3-dimethylamino-3-(6-methoxyimidazo[1,2-*b*]pyridazinyl-3)propenoate (**10f**).

A mixture of sodium methoxide in methanol (0.16 g of sodium in 8 ml of methanol) and 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]-6-chloroimidazo[1,2-*b*]pyridazine (**9f**, 0.736 g, 0.002 mole) was heated under reflux for 4 hours. The solvent was evaporated *in vacuo* and water (4 ml) was added. The precipitate was collected by filtration and recrystallized from ethanol to give **10f** in 82% yield, mp 204-206°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 2.77 (6H, s, $N(CH_3)_2$), 3.22 (3H, s, OCH_3), 3.95 (3H, s, $COOCH_3$), 6.99 (1H, d, H_7), 7.42-7.66 (3H, m, Ph), 7.69 (1H, s, H_2), 7.93-8.09 (2H, m, Ph), 8.13 (1H, d, H_8), 9.59 (1H, br s, NHCO), $J_{H7H8} = 9.6$ Hz, when deuterium oxide was added the singlet at δ = 9.59 disappeared.

Anal. Calcd. for $C_{20}H_{21}N_5O_4$: C, 60.75; H, 5.35; N, 17.71. Found: C, 60.54; H, 5.35; N, 17.75.

Methyl 2-Benzoylamino-3-dimethylamino-3-(imidazo[2,1-*b*]thiazolyl-5)propenoate (**10g**).

A mixture of sodium methoxide in methanol (0.065 g of sodium in 3 ml of methanol) and 5-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]imidazo[2,1-*b*]thiazole (**9g**, 0.17 g, 0.0005 mole) was left at room temperature for 20 hours. To the mixture water (7 ml) was added and extracted with dichloromethane (3 times, 10 ml each time). The organic layer was evaporated *in vacuo* and acetone was added. The precipitate was collected by filtration and recrystallized from acetone to give **10g** in 84% yield, mp 178-180°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 2.80 (6H, s, $N(CH_3)_2$), 3.32 and 3.63 (3H, 2 s (3:1), OCH_3), 7.31-7.70 (5H, m, Ph, H_2, H_6), 7.79 (1H, d, H_3), 7.92-8.17 (2H, m, Ph), 9.26 and 9.50 (1H, 2 br s (1:3), NHCO), $J_{H2H3} = 4.4$ Hz, when deuterium oxide was added the singlets at δ = 9.26 and δ = 9.50 disappeared.

Anal. Calcd. for $C_{18}H_{18}N_4O_3S$: C, 58.36; H, 4.90; N, 15.12. Found: C, 58.09; H, 4.67; N, 15.24.

3-[(Phenyl-5-oxo-2-oxazolin-4-ylidene)(methoxy)methyl]-6-chloroimidazo[1,2-*b*]pyridazine (**11**).

A mixture of 3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyliden-4)methyl]-6-chloroimidazo[1,2-*b*]pyridazine (**9f**, 0.184 g, 0.0005 mole), methanol (3 ml) and sulfuric acid (98%, 0.3 ml) was heated under reflux for 2 hours. The solvent was evaporated *in vacuo* and water (2 ml) was added to the residue. The precipitate was collected by filtration and recrystallized from a mixture of methanol and chloroform to give **11** in 45% yield, mp 245-247°; ^{1}H nmr (deuteriochloroform, 60 MHz): δ 4.01 (3H, s, OCH_3), 7.23 (1H, d, H_7), 7.48-7.67 (3H, m, Ph), 8.07 (1H, d, H_8), 8.11-8.37 (2H, m, Ph), 8.68 (1H, s, H_2), $J_{H7H8} = 9.3$ Hz.

Anal. Calcd. for $C_{17}H_{11}ClN_4O_3$: C, 57.56; H, 3.13; N, 15.79. Found: C, 57.23; H, 2.91; N, 15.88.

The Synthesis of 3-Benzoylaminoacetylimidazo[1,2-*x*]azines **12**. General Procedure.

A mixture of compound **9** (0.001 mole), methanol (2 ml) and hydrochloric acid (36%, 2 ml) was heated under reflux. The reaction was followed by tlc (DC-Alufolien Kiesegel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol, 5:1, as solvent). The solvent was evaporated *in vacuo*. To the oily residue saturated solution of sodium hydrogen carbonate was added until the evolution of carbon dioxide ceased and extracted with chloroform (3 times, 8 ml each time). The organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo* and the residue was recrystallized from an appropiate solvent to give **12a-g**.

In the same manner, the following compounds were prepared:

3-Benzoylaminoacetylimidazo[1,2-*a*]pyridine (**12a**).

This compound was prepared from **9a**, 1 hour reflux in 57% yield, mp 152-154° (from a mixture of diisopropyl ether and

methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide, 60 MHz): δ 4.73 (2H, d, CH_2NH), 7.16-7.70 (5H, m, Ph, H_6, H_7), 7.75-8.10 (3H, m, Ph, H_8), 8.82 (1H, s, H_2), 8.99 (1H, br t, CH_2N*H*), 9.54 (1H, dd, H_5), J_{CHNH} = 6 Hz, J_{H5H6} = 7 Hz, J_{H5H7} = 1 Hz, when deuterium oxide was added the broad triplet at δ = 8.99 disappeared and the doublet at δ = 4.73 changed into a singlet.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04. Found: C, 68.53; H, 4.51; N, 14.96.

3-Benzoylaminoacetyl-7-methylimidazo[1,2-*a*]pyridine (**12b**).

This compound was prepared from **9b**, 0.5 hour reflux in 42% yield, mp 188-190° (from methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 2.45 (3H, s, CH_3), 4.68 (2H, d, CH_2NH), 7.15 (1H, dd, H_6), 7.47-7.57 (3H, m, Ph), 7.66 (1H, br s, H_8) 7.90-7.93 (2H, m, Ph), 8.72 (1H, s, H_2), 8.94 (1H, br t, CH_2N*H*), 9.38 (1H, d, H_5), J_{CHNH} = 5.65 Hz, J_{H5H6} = 7.15 Hz, J_{H6H8} = 1.51 Hz.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.47; H, 5.17; N, 14.20.

3-Benzoylaminoacetyl-8-nitroimidazo[1,2-*a*]pyridine (**12c**).

This compound was prepared from **9c**, (1 hour and 15 minutes reflux), in 34% yield, mp 218-221° (from a mixture of methanol and water); ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 4.77 (2H, d, CH_2NH), 7.47 (1H, dd, H_6), 7.49-7.60 (3H, m, Ph), 7.91-7.94 (2H, m, Ph), 8.59 (1H, dd, H_7), 8.99 (1H, s, H_2), 9.81 (1H, dd, H_5), 9.02 (1H, br t, CH_2N*H*), J_{CHNH} = 6.03 Hz, J_{H5H6} = 6.79 Hz, J_{H5H7} = 1.13 Hz, J_{H6H7} = 7.53 Hz.

Anal. Calcd. for $C_{16}H_{12}N_4O_4$: C, 59.25; H, 3.73; N, 17.28. Found: C, 58.98; H, 3.75; N, 17.25.

3-Benzoylaminoacetyl-6-chloroimidazo[1,2-*a*]pyridine (**12d**).

This compound was prepared from **9d**, 1 hour reflux, in 54% yield, mp 191-193° (from methanol); ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 4.72 (2H, d, CH_2NH), 7.48-7.60 (3H, m, Ph), 7.75 (1H, dd, H_7), 7.94 (1H, dd, H_8), 7.90-7.93 (2H, m, Ph), 8.84 (1H, s, H_2), 8.98 (1H, br t, CH_2N*H*), 9.57 (1H, dd, H_5), J_{CHNH} = 5.65 Hz, J_{H5H7} = 2.26 Hz, J_{H5H8} = 0.75 Hz, J_{H7H8} = 9.42 Hz.

Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.25; H, 3.86; N, 13.39. Found: C, 61.40; H, 3.89; N, 13.37.

3-Benzoylaminoacetylimidazo[1,2-*b*]pyridazine (**12e**).

This compound was prepared from **9e**, 1 hour reflux, crystallized from methanol and recrystallized from acetonitrile to give **12e** in 16% yield, mp 170-172°; ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 4.82 (2H, d, CH_2NH), 7.48-7.57 (3H, m, Ph), 7.55 (1H, dd, H_7) 7.90-7.93 (2H, m, Ph), 8.36 (1H, dd, H_8), 8.67 (1H, s, H_2), 8.82 (1H, dd, H_6), 8.89 (1H, br t, CH_2N*H*), J_{CHNH} = 5.65 Hz, J_{H6H7} = 4.52 Hz, J_{H6H8} = 1.51 Hz, J_{H7H8} = 9.42 Hz.

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.42; H, 4.38; N, 19.92.

3-Benzoylaminoacetyl-6-chloroimidazo[1,2-*b*]pyridazine (**12f**).

This compound was prepared from **9f**, 1 hour reflux, in 38% yield, mp 171-174° (from acetonitrile); ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 4.78 (2H, d, CH_2NH), 7.48-7.64 (3H, m, Ph), 7.69 (1H, d, H_7) 7.90-7.93 (2H, m, Ph), 8.44 (1H, d, H_8), 8.73 (1H, s, H_2), 8.92 (1H, br t, CH_2N*H*), J_{CHNH} = 5.65 Hz, J_{H7H8} = 9.42 Hz.

Anal. Calcd. for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.17; H, 3.30; N, 17.77.

5-Benzoylaminoacetylimidazo[2,1-*b*]thiazole (**12g**).

This compound was prepared from **9g**, 50 minutes of reflux, crystallized from methanol and recrystallized from acetonitrile and gave **12g** in 44% yield, mp 148-150°; ms: 285.057199 (M^+, $C_{14}H_{11}N_3O_2S$); ^{1}H nmr (dimethyl-d_6 sulfoxide, 300 MHz): δ 4.60 (2H, d, CH_2NH), 7.45-7.60 (3H, m, Ph), 7.57 (1H, dd, $H_{2\ or\ 3}$), 7.87-7.94 (2H, m, Ph), 8.32 (1H, d, $H_{2\ or\ 3}$), 8.43 (1H, d, H_6), 8.95 (1H, br t, CH_2N*H*), J_{CHNH} = 5.65 Hz, J_{H2H3} = 4.3 Hz, J = 1.2 Hz.

Anal. Calcd. for $C_{14}H_{11}N_3O_2S{\bullet}H_2O$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.34; H, 4.14; N, 13.79.

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