

Lucija Jukić [a], Anton Čopar [a], Mateja Malešič [b], Aleš Krbavčič [b],
Jurij Svete [a], and Branko Stanovnik* [a]

[a] Faculty of Chemistry and Chemical Technology, University of Ljubljana, 1000 Ljubljana, Slovenia

[b] Faculty of Pharmacy, University of Ljubljana, 1000 Ljubljana, Slovenia

Received March 15, 1999

Some 3-substituted pyrrolo[1,2-*a*]azines **4a-d** were prepared in low yields from the corresponding 2-methylpyridines **1a,b** and pyrazine derivatives **1c,d** by quaternization with methyl bromoacetate followed by treatment with *N,N*-dimethylformamide dimethyl acetal. Ethyl 2-pyridinylacetate (**5**) and 2-pyridinylacetonitrile (**6**) were converted with 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**9**) into pyrrolo[1,2-*a*]pyridine derivatives **10** and **12**, intermediates in the synthesis of azaaplysinopsins.

J. Heterocyclic Chem., **36**, 1147 (1999).

The 3-substituted azolo[1,2-*x*]azines have been prepared by intramolecular cyclization of pyridinium allylides [1] and by intramolecular aldol condensation of acyl and ethoxycarbonyl methines [2]. The reactions of pyridines and pyridinium methylides with alkynic esters provide a useful synthesis of indolizines containing ester groups in the five-membered ring. Since the reactions of 1,3-dipoles as well as dipolarophiles are dependent on the electronic and steric effects, the substituents in the 1, 2, and 3 positions of the indolizine nucleus are restricted mostly to electron withdrawing and relatively small groups. If unsymmetrical dipolarophiles are employed, a mixture of two possible isomers is often formed [3]. Carboxylic or ester group can be introduced at position 3 in indolizine system with ethyl chloroformate [4].

3-Acyl substituted imidazo[1,2-*x*]azines are formed by treatment of *N,N*-dimethyl-*N'*-heteroarylformamidines with α -haloketones [5], while the corresponding 3-acylpyrrolo[1,2-*a*]azines are prepared by quaternization of α -methylazines, in order to activate the methyl group, with α -haloketones followed by treatment with *N,N*-dimethylformamide dimethyl acetal [6]. However, since *N,N*-dimethylformamide dimethyl acetal is an excellent

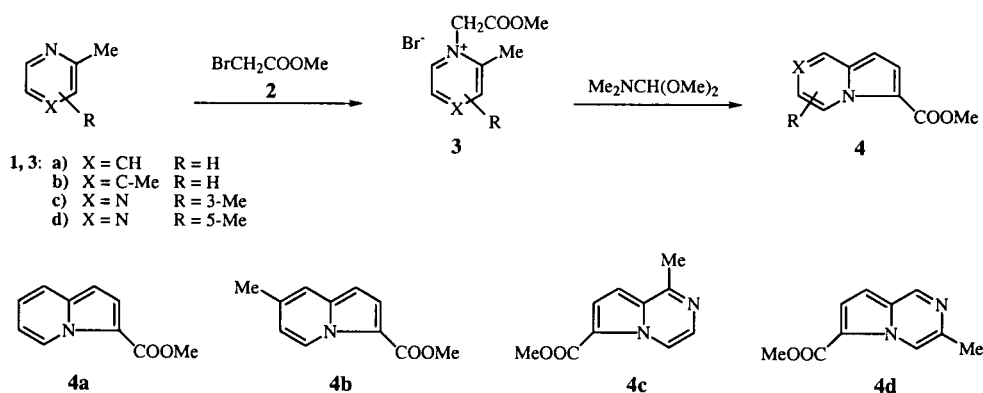
dehydrating agent, a concurrent reaction produces 2-substituted pyrrolo[1,2-*x*]azines, in some instances as the major products [6]. The reaction has been employed for preparation of 3-acetyl- and 3-benzoylpyrrolo[1,2-*a*]pyridines, 7-benzoyl-3-methylpyrrolo[1,2-*c*]pyrimidine and 6-benzoyl-1-methylpyrrolo[1,2-*a*]pyrazine.

When 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone has been employed instead of an α -haloketone fused imidazole with oxazolone ring connected through a double bond conjugated to imidazole system has been formed in one step [7].

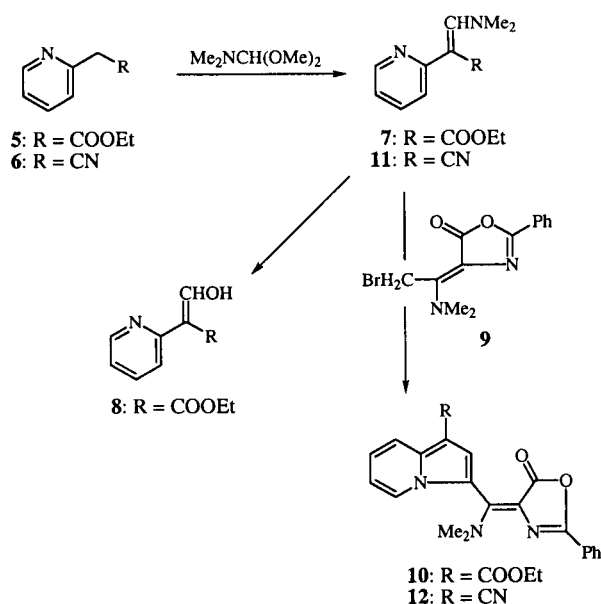
This latest reaction represents an alternative and simplified method for preparation of azaaplysinopsins in comparison with other methods based on the coupling of an heteroaromatic aldehyde and an appropriately substituted hydantoin [8,9], and Standing/aza-Wittig reaction followed by electrocyclic ring closure [10,11].

In this communication we report on some attempts to prepare 3-substituted pyrrolo[1,2-*x*]azines. First, 2-methylpyridine (**1a**), 2,4-dimethylpyridine (**1b**), 2,3-dimethylpyrazine (**1c**) or 2,5-dimethylpyrazine (**1d**) was converted with methyl bromoacetate to give the corresponding quaternary salts **3**. They were without further

Scheme 1



Scheme 2



purification treated with *N,N*-dimethylformamide dimethyl acetal to give a mixture, from which products were isolated in low yields: methyl pyrrolo[1,2-*a*]pyridine-3-carboxylate (**4a**) in 23%, methyl 7-methylpyrrolo[1,2-*a*]pyridine-3-carboxylate (**4b**) in 6%, methyl 1-methylpyrrolo[1,2-*a*]pyrazine-6-carboxylate (**4c**) in 2.8%, and methyl 3-methylpyrrolo[1,2-*a*]pyrazine-6-carboxylate (**4d**) in 2.2% yield. 2,6-Dimethylpyridine, 2-methylquinoline and 2,6-dimethylquinoline gave under the same reaction conditions only tarry material from which the corresponding products could not be isolated.

In an attempt to prepare some intermediates in the synthesis of aplysinopsin derivatives ethyl 2-pyridinylacetate (**5**) and 2-pyridinylacetonitrile (**6**) were first transformed with *N,N*-dimethylformamide dimethyl acetal into ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**7**) and 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**11**) according to the procedure described earlier [12]. Compound **7** hydrolysed by standing at room temperature

to give ethyl 3-hydroxy-2-(pyridinyl-2)propenoate (**8**), therefore the crude **7** was used immediately in further reaction.

In the reactions of compounds **7** and **11** with 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**9**), 1-ethoxycarbonyl-3-[(dimethylamino)-(2-phenyl-5-oxo-2-oxazolonylidene-4)methyl]pyrrolo[1,2-*a*]pyridine (**10**) and 1-cyano derivative **12** were formed in 31% and 16% yields, while 2-aminothiazole has been transformed according to this methodology into 3-acylimidazo[2,1-*b*]thiazole [13].

2-Methyl-4,5-dihydrothiazole (**13**) gave with *t*-butoxybis(dimethylamino)methane 2-(2-dimethylaminoethylidene)-4,5-dihydrothiazole (**14**), which was further transformed with bromoacetophenone (**15**) into 3-benzoylmethyl-2-(2-dimethylaminoethenyl)-4,5-dihydrothiazolium bromide (**16**). All attempts to transform it into 3-benzoyl-2,3-dihydropyrrolo[2,1-*b*]thiazole (**17**) failed.

EXPERIMENTAL

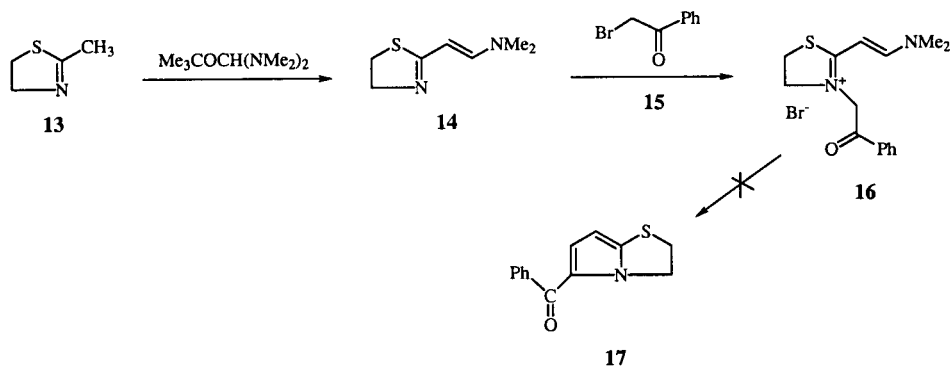
Melting points were taken on a Kofler micro hot stage. The ¹H nmr spectra were obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer in such solvent as dimethyl-*d*₆ sulfoxide and deuteriochloroform with tetramethylsilane as the internal standard. The ir spectra were obtained on a Perkin-Elmer 1310 spectrometer. The microanalyses for C, H and N were obtained on a Perkin-Elmer CHN Analyser 2400. Mass spectra were obtained on an AutoSpec Q spectrometer.

Ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**7**) and 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**11**) were prepared by the procedures described in the literature [12].

Methyl Pyrrolo[1,2-*a*]pyridine-3-carboxylate (**4a**).

2-Methylpyridine (**1a**, 0.94 g, 1 mmole) and methyl bromoacetate (**2**, 1.53 g, 1 mmole) were heated at 80° for 90 minutes. The quaternary salt obtained was dissolved without further purification in 10 ml of *N,N*-dimethylformamide, 2.4 ml of *N,N*-dimethylformamide dimethyl acetal was added and heated under reflux for 2 hours. The solvent was evaporated, and the residue was purified by the column chromatography (silica gel and

Scheme 3



ether/petroleum ether 1:3 as the solvent) to give **4a** in 23% yield, corresponding to the compound obtained previously [14].

By the same procedure compounds **4b-d** were prepared:

Methyl 7-Methylpyrrolo[1,2-*a*]pyridine-3-carboxylate (**4b**).

This compound was prepared from 2,4-dimethylpyridine (**1b**) in 6% yield, mp 33-34° dec (from hexane); ¹H nmr (deuteriochloroform): δ 2.32 (s, 3H, 7-Me), 3.84 (s, 3H, OMe), 6.32 (d, 1-H), 6.60 (dd, 6-H), 7.20 (dd deg, 8-H), 7.47 (d, 2-H), 9.24 (d, 5-H), J_{1,2} = 4.5 Hz, J_{5,6} = 7 Hz, J_{5,8} = 1.5 Hz.

Anal. Calcd. for C₁₁H₁₁NO₂: C, 69.83; H, 5.81; N, 7.40. Found: C, 70.15; H, 5.93; N, 7.28.

Methyl 1-Methylpyrrolo[1,2-*a*]pyrazine-6-carboxylate (**4c**).

This compound was prepared from 2,3-dimethylpyrazine (**1c**) in 2.8% yield, mp 110-113° dec (from heptane); ¹H nmr (deuteriochloroform): δ 2.72 (s, 3H, 1-Me), 3.83 (s, 3H, OMe), 6.67 (d, 8-H), 7.40 (d, 7-H), 7.66 (d, 3-H), 8.96 (d, 4-H), J_{3,4} = 5 Hz, J_{8,9} = 4 Hz.

Anal. Calcd. for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.16; H, 5.22; N, 14.39.

Methyl 3-Methylpyrrolo[1,2-*a*]pyrazine-6-carboxylate (**4d**).

This compound was prepared from 2,5-dimethylpyrazine (**1d**) in 2.2% yield, mp 73-74° dec (from heptane); ¹H nmr (deuteriochloroform): δ 2.54 (s, 3H, 3-Me), 3.95 (s, 3H, OMe), 6.69 (d, 8-H), 7.42 (d, 7-H), 8.85 and 9.00 (s, s, 1,4-H), J_{8,9} = 4 Hz.

Anal. Calcd. for C₁₀H₁₀N₂O₂: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.16; H, 5.08; N, 14.82.

Ethyl 3-Hydroxy-2-(pyridinyl-2)propenoate (**8**).

To a solution of ethyl 2-pyridinylacetate (**5**, 0.2 g, 1.2 mmoles) in toluene (3 ml) *N,N*-dimethylformamide dimethyl acetal (0.8 ml, 6 mmoles) was added and the mixture was heated under reflux for 2 hours. Reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol 25:1 as the solvent). The volatile compounds were evaporated *in vacuo*. When the oily residue was allowed to stand at room temperature, ethyl 3-dimethylamino-2-(pyridinyl-2)propenoate (**7**) hydrolysed into 3-hydroxy-2-(pyridinyl-2)propenoate (**8**), mp 96-97° dec (from water); ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 1.26 (t, 3H, COOCH₂CH₃), 4.17 (q, 2H, COOCH₂CH₃), 7.22 (ddd, 1H, H₅), 8.04 (ddd, 1H, H₄), 8.35 (dd, 1H, H₆), 8.54 (dd, 1H, H₃), 9.65 (s, 1H, CHO), J_{3,4} = 9.0 Hz, J_{3,5} = 1.1 Hz, J_{4,5} = 7.2 Hz, J_{4,6} = 1.4 Hz, J_{5,6} = 6.1 Hz, J_{CH₂CH₃} = 7.1 Hz.

Anal. Calcd. for C₁₀H₁₁NO₃: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.10; H, 5.65; N, 7.33.

1-Ethoxycarbonyl-3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyldene-4)methyl]pyrrolo[1,2-*a*]pyridine (**10**).

To a solution of ethyl 2-pyridinylacetate (**5**, 0.2 g, 1.2 mmoles) in toluene (3 ml) *N,N*-dimethylformamide dimethyl acetal (0.8 ml, 6 mmoles) was added and the mixture was heated under reflux for 2 hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol 25:1 as the solvent). The volatile compounds were evaporated *in vacuo*. The oily residue was dissolved in *N,N*-dimethylformamide (2 ml) and 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**9**, 0.3 g, 1 mmole) was added. The reaction mixture was allowed to stand at room temperature for 5 days and then heated for 3 hours under reflux.

The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and diethyl ether as the solvent). After that the solvent was evaporated *in vacuo* and water (2 ml) was added to give **10** in 31% yield, mp 113-115° dec (ethanol); ms: m/z 403 (M⁺); ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 1.33 (t, 3H, COOCH₂CH₃), 3.37 (s, 6H, N(CH₃)₂), 4.30 (q, 2H, COOCH₂CH₃), 7.00 (ddd, 1H, H₆), 7.18-7.55 (m, 6H, H₇, Ph), 7.68 (s, 1H, H₂), 7.91 (m, 1H, H₈), 8.20 (dd, 1H, H₅), J_{5,6} = 7 Hz, J_{5,7} = 1 Hz, J_{6,7} = 7 Hz, J_{6,8} = 1.5 Hz, J_{CH₂CH₃} = 7 Hz.

Anal. Calcd. for C₂₃H₂₁N₃O₄: C, 68.48; H, 5.25; N, 10.42. Found: C, 67.72; H, 5.19; N, 10.19.

1-Cyano-3-[(dimethylamino)(2-phenyl-5-oxo-2-oxazolinyldene-4)methyl]pyrrolo[1,2-*a*]pyridine (**12**).

To a solution of 3-dimethylamino-2-(pyridinyl-2)propenonitrile (**11**, 0.16 g, 0.9 mmole) in *N,N*-dimethylformamide (2 ml) 4-(2-bromo-1-dimethylaminoethylidene)-2-phenyl-5(4*H*)-oxazolone (**9**, 0.3 g, 0.9 mmole) was added. The reaction mixture was allowed to stand at room temperature for 4 days with occasional shaking and then heated under reflux for 2 hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and diethyl ether as the solvent). After that the solvent was evaporated *in vacuo* and methanol/*n*-hexane (2 ml) was added to precipitate **12** in 16% yield, mp 223-225° dec (ethanol); ir: 2200 cm⁻¹; ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 2.50 (rs, 6H, N(CH₃)₂), 7.02 (ddd, 1H, H₆), 7.33-7.41 (m, 1H, H₇), 7.51-7.53 (m, 3H, Ph), 7.54 (s, 1H, H₂), 7.78 (d, 1H, H₈), 7.87-7.91 (m, 2H, Ph), 8.26 (d, 1H, H₅), J_{5,6} = 6.9 Hz, J_{6,7} = 6.8 Hz, J_{6,8} = 1.2 Hz, J_{7,8} = 7.9 Hz.

Anal. Calcd. for C₂₁H₁₆N₄O₂: C, 70.78; H, 4.53; N, 15.72. Found: C, 70.63; H, 4.33; N, 15.38.

2-(2-Dimethylaminoethylidene)-4,5-dihydrothiazole (**14**).

To a solution of 2-methyl-4,5-dihydrothiazole (**13**, 2.5 g, 25 mmoles) in *N,N*-dimethylformamide (10 ml), under an atmosphere of argon, *t*-butoxybis(dimethylamino)methane (Bredereck's reagent) (3.75 g, 21.5 mmoles) was added. The mixture was heated at 110° for 6 hours. After cooling, the dark reaction mixture was poured into water and extracted with 3 portions of 15 ml of methylene chloride. The organic layer was washed with 3 portions of 15 ml of water and dried over magnesium sulphate. The volatile components were evaporated *in vacuo* and the residue recrystallized from diisopropyl ether to give **14** in 31% yield, mp 104-106° dec; ms: m/z 156 (M⁺); ¹H nmr (deuteriochloroform): δ 2.86 (s, 6H, N(CH₃)₂), 3.20 (t, 2H, 5-CH₂), 4.18 (t, 2H, 4-CH₂), 5.20 (d, 1H, CH), 6.92 (d, 1H, CH), J_{4CH₂-5CH₂} = 7.74 Hz, J_{CH=CH} = 13.26 Hz.

Anal. Calcd. for C₇H₁₂N₂S: C, 53.35; H, 7.69; N, 17.95. Found: C, 53.74; H, 7.77; N, 18.03.

3-Benzoylmethyl-2-(2-dimethylaminoethenyl)-4,5-dihydrothiazolium Bromide (**16**).

The solution of **14** (0.16 g, 1 mmole) and bromoacetophenone (**15**) in *N,N*-dimethylformamide (1.5 ml) was stirred at room temperature for 24 hours. The precipitate was collected by filtration and recrystallized from the mixture of ethanol and water to give **16** in 48% yield, mp 150-152° dec; ms: m/z 275 (MH⁺-Br); ¹H nmr (dimethyl-*d*₆ sulfoxide): δ 3.00 (s, 3H, NCH₃), 3.29 (s, 3H, NCH₃), 3.50 (t, 2H, 5-CH₂), 4.08 (t, 2H, 4-CH₂), 5.52 (s, 2H, CH₂CO), 5.60 (d, 1H, =CH), 7.59-7.74 (m, 3H, PhCO), 7.85 (d, 1H, =CH), 8.00-8.03 (m, 2H, PhCO), J_{4CH₂-5CH₂} = 7.63 Hz, J_{CH=CH} = 11.90 Hz.

Anal. Calcd. for $C_{15}H_{19}N_2OSBr$: C, 50.71; H, 5.39; N, 7.88.
Found: C, 50.49; H, 5.60; N, 7.80.

Acknowledgement.

The financial support of the Ministry for Science and Technology, Slovenia, is fully acknowledged.

REFERENCES AND NOTES

- [1] T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Tetrahedron*, **28**, 4947 (1972).
- [2] T. Melton and D. G. Wibberley, *J. Chem. Soc. (C)*, 983 (1967).
- [3] For reviews see: [a] H. L. Blewitt, Indolizine and Aza Derivatives with Additional Nitrogen in the 5-Membered Ring, in: *Special Topics in Heterocyclic Chemistry*, A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, New York, 1977, pp 117-178; [b] G. Maury, Azaindolizine Systems Having More Than One Nitrogen Atom in the 6-Membered Ring, in: *Special Topics in Heterocyclic Chemistry*, A. Weissberger and E. C. Taylor, eds, John Wiley and Sons, New York, 1977, pp 179-244.
- [4] For a review see: F. J. Swinbourne, J. H. Hunt, and G. Klinkert, *Adv. Heterocyclic Chem.*, **23**, 103 (1978).
- [5] S. Podergajs, B. Stanovnik, and M. Tišler, *Synthesis*, 263 (1984).
- [6] A. Čopar, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, **30**, 1577 (1993).
- [7] U. Bratušek, A. Hvala, and B. Stanovnik, *J. Heterocyclic Chem.*, **35**, 971 (1998).
- [8] E. Ware, *Chem. Rev.*, **46**, 403 (1950).
- [9] G. Guella, I. Mancini, H. Zibrowius, and F. Pietra, *Helv. Chim. Acta*, **72**, 1444 (1989).
- [10] P. Molina and M. J. Vilaplana, *Synthesis*, 1197 (1994).
- [11] P. Molina, P. Almendros, and P. M. Fresneda, *Tetrahedron*, **50**, 2241 (1994).
- [12] L. Jukič, U. Bratušek, M. Škof, J. Svete, and B. Stanovnik, *Khim. Geterotsikl. Soed.*, 1510 (1996).
- [13] S. Fajgelj, B. Stanovnik, and M. Tišler, *Heterocycles*, **24**, 379 (1986).
- [14] G. Jones and J. Stanyer, *J. Chem. Soc. (C)*, 901 (1969).