

PREPARATION OF AZA-ANALOGS OF APLYSINOPSINS AND ZWITTERIONIC BY REACTIONS OF HETEROCUMULENES IN NAPHTHYRIDINE'S SERIES

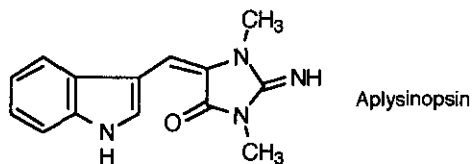
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Abstract - Imidazo[1,2-*a*][1,8]naphthyridines (**9a,b**) having the carbodiimide moiety on the position 1 lead to (*Z*)-aza-aplysinopsins (**10a,b**) by solid supported reaction on neutral alumina. By flash chromatography these heterocumulenes are stereospecifically converted to the corresponding methoxyimidazol-4-ones (**11a,b**) in good yields. In contrast, tandem aza-Wittig-cyclization reaction of imidazo[1,2-*a*][1,8]naphthyridine (**13**) having iminophosphorane moiety on the position 2 gives zwitterionic compounds (**14a,b**, **15**) by *N*-annulation under thermal conditions.

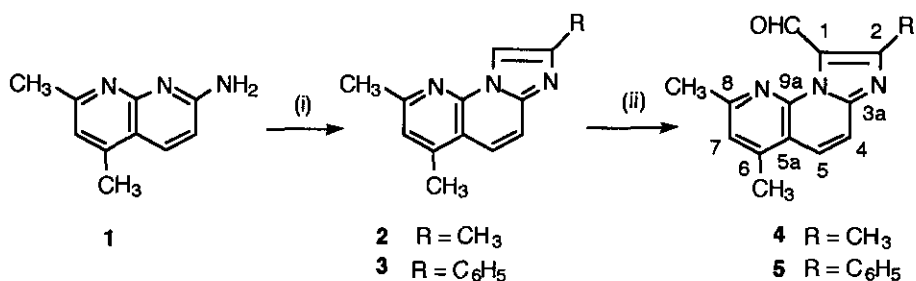
The syntheses of marine product, e.g. aplysinopsin isolated from the sponge *Aplysinopsis reticulata* (Dictyoceratida),¹ have been intensively investigated during the last past decade. Indeed, these molecules

have important biological activities such as specific cytotoxicity against cancer cells,² neurotransmitting³ or antimicrobial activity.⁴



Various methods for the preparation of methyleneimidazolidin-2,4-diones have been developed but they often afforded aplysinopsins in poor yields and as a mixture of (*E*)- and (*Z*)- isomers.⁵ A recent attractive approach for this preparation was performed by aza-Wittig reaction of vinyliminophosphoranes with isocyanate and then by electrocyclization of the resultant heterocumulene.⁶ Insertion of nitrogen atom to the aplysinopsin molecule can enhance pharmacological activity,⁷ so in the course of searching for new antiviral compounds, we report here stereoselective annulation of heterocumulenes in imidazonaphthyridine series to prepare aza- and zwitterionic analogs of aplysinopsin.

The synthesis of 1-formyl-2,6,8-trimethylimidazo[1,2-*a*][1,8]naphthyridine and 6,8-dimethyl-1-formyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridine (**4**, **5**) was accomplished by a Vilsmeier-Haack's reaction of requisite 2,6,8-trimethylimidazo[1,2-*a*][1,8]naphthyridine and 2-phenylimidazo[1,2-*a*][1,8]naphthyridine (**2**, **3**⁸) obtained by condensation of 2-amino-5,7-dimethyl[1,8]naphthyridine (**1**)⁹ with appropriate α -halogeno ketones (Scheme 1).

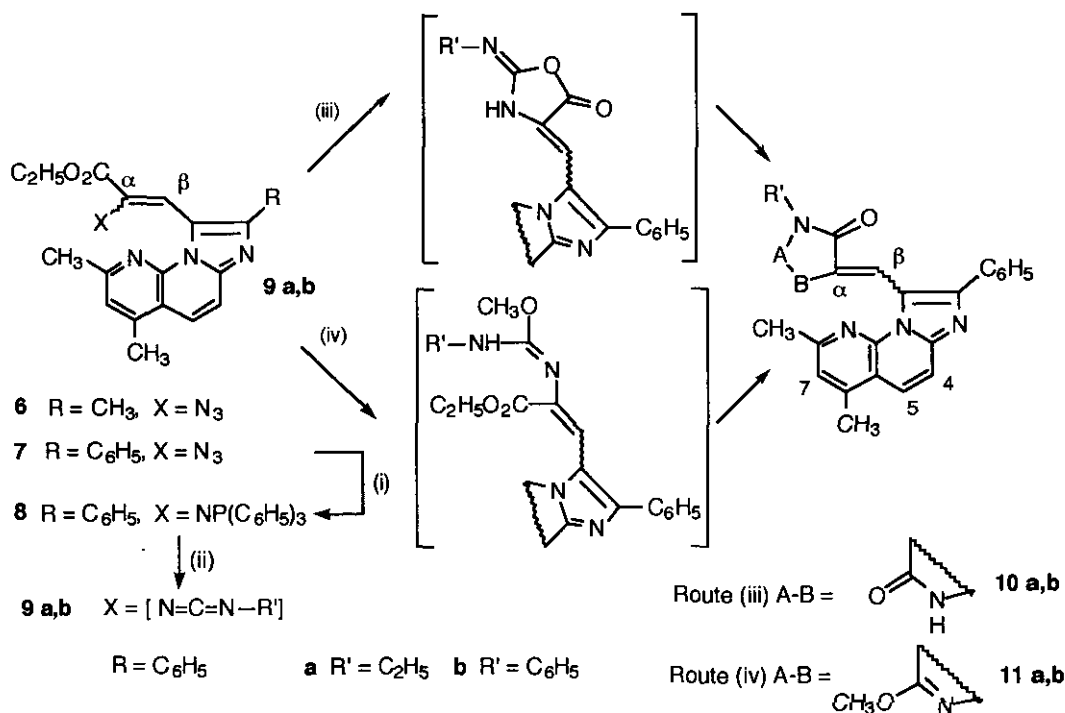


Reagents and conditions : (i) ClCH₂COR, C₂H₅OH, reflux ; (ii) POCl₃/DMF, Δ

Scheme 1

Azidovinyls (**6**, **7**) were prepared by classical condensation of the corresponding aldehyde (**4** or **5**) with ethyl azidoacetate in the presence of sodium ethoxide at -30°C ¹⁰ (Scheme 2). The most relevant ¹H nmr data of **6**, **7** are the signal at δ 8.28 or δ 8.58 assigned to H- β of each compound but we could not assign its stereochemistry due to their high instability. The preparation of vinyliminophosphorane (**8**) was achieved by Staudinger's reaction¹¹ of the corresponding azidovinyl (**7**) with triphenylphosphine in

methylene chloride in 50 % yield. The (*Z*)-configuration of **8** was given in regard with the value of $^2J_{P-C}$ for C- β and as well as the low value of the heteronuclear coupling constant $^3J_{H-C\beta-CO} = 4$ Hz.¹² Owing to the low solubility towards the solvent employed, the conversion to the corresponding vinyliminophosphorane of the aldehyde (**4**) was unsuccessful. We now turned our attention to aza-Wittig reaction of **8**. We could expect a C- or N-annulation of the intermediate heterocumulene. Treatment of the vinyliminophosphorane (**8**) in toluene at 50°C for 6 h with ethyl isocyanate (or at room temperature for 2 h with phenyl isocyanate) gave the corresponding carbodiimides (**9a,b**). These compounds were not purified but their presence were supported by the fact that ir spectra showed a $\nu_{N=C=N}$ at 2100 cm^{-1} . Finally, (*Z*)-aza-aplysinopsins derivatives (**10a,b**) were obtained from **9a,b** in poor yields by thermal cyclization in 1,6-dibromohexane. The compounds (**10a,b**) result from intramolecular cyclization across the ester function of intermediate azalactones which undergo Dimroth rearrangement. Furthermore, we have observed that the carbodiimides (**9a,b**) react with methanol to give a ratio of 85/15 of (*Z/E*)-methoxy compounds (**11a,b**) via isourea derivatives, the structures of which were confirmed by the appearance of methoxy signals at δ 3.44 - 4.17 ppm in ^1H -nmr spectrum.



Reagents and conditions : (i) P(C₆H₅)₃, CH₂Cl₂ ; (ii) R'NCO, toluene ; (iii) Neutral Al₂O₃, CH₂Cl₂ or C₆H₁₀Br₂, reflux ; (iv) Neutral Al₂O₃, CH₃OH or CH₃OH, reflux.

Scheme 2

Interestingly, when a solution of **9a,b** in methylene chloride was settled down on a neutral alumina column for 15 min, and then eluted with methanol, the (*Z*)-hydantoin (**10a,b**) were produced in high yields. Under the same procedure, but with a flash chromatography using methanol as eluent, the (*Z*)-compounds (**11a,b**) were obtained in 47 and 42% yields, respectively. (Scheme 2)

This solid supported reaction of the heterocumulenes proceeded smoothly and stereoselectively. The (*Z*)-stereochemistry¹³ of **10a,b** was secured by interpretation of NOE's experiments. (Figure 1 for **10a**)

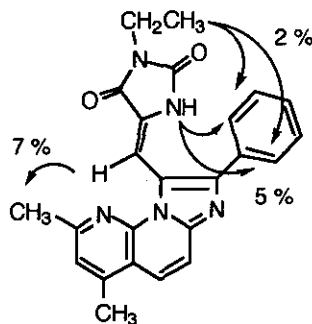
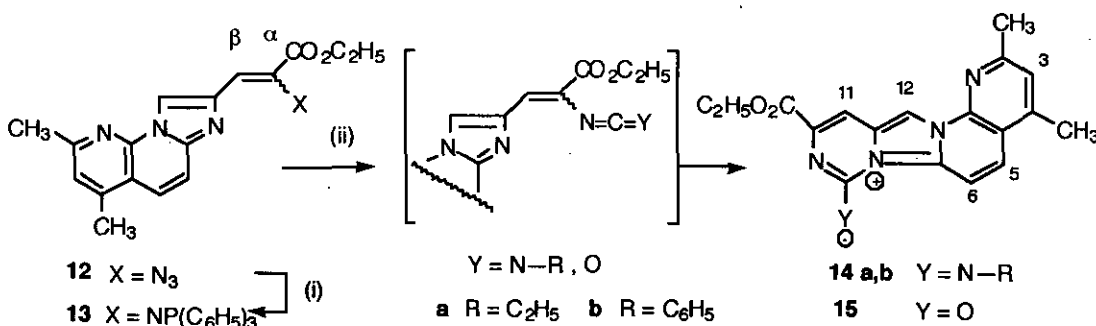


Figure 1

In contrast, when the iminophosphorane (**13**) obtained from **12**¹⁰ was treated with ethyl (or phenyl) isocyanate under the same conditions, zwitterionic compounds (**14a,b**) and (**15**) resulting from a *N*-annulation of the intermediate heterocumulenes were obtained in 63, 56 and 21% yields, respectively. The formation of the zwitterionic compound (**15**) can be explained in terms of the formation of the isocyanate intermediate during the reaction.¹⁴ Mass spectrometric analysis and ¹H, ¹³C HMBC and HMQC-TOCSY nmr data of **14a,b** and **15** were consistent with those tetracyclic structures. The highly deshielding proton H-C(6) at $\delta = 9.30 - 9.90$ for **14a,b** and **15** is a good indication of a *peri* effect due to $\ominus Y-C(8)$. (Scheme 3).



Reagents and conditions : (i) $P(C_6H_5)_3$, CH_2Cl_2 ; (ii) $RNCO$, toluene, reflux

Scheme 3

ACKNOWLEDGEMENTS

We thank C. Roumestan for structural determinations.

EXPERIMENTAL

General. All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. Ir spectra were obtained on a BECKMAN Acculab 2 spectrophotometer. ^1H - and ^{13}C -nmr spectra were recorded on a Bruker AC-400 spectrometer working at 400 MHz (^1H) and 100 MHz (^{13}C). Chemical shift data are reported in ppm downfield δ from TMS. Coupling constants, J , are given in Hz ; s, d, t, m, indicate singlet, doublet, triplet, and multiplet, respectively. Mass spectroscopy was performed on HEWLETT PACKARD 5989 A instruments. Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier (France). 2-Amino-5,7-dimethyl[1,8]naphthyridine (**1**)⁹ and 2-phenylimidazo[1,2-*a*][1,8]naphthyridine (**3**)⁸ are known compounds. Ethyl α -azido- β -(6,8-dimethylimidazo[1,2-*a*][1,8]naphthyridin-2-yl)propenoate (**12**) was prepared according to the literature procedure.¹⁰

2,6,8-Trimethylimidazo[1,2-*a*][1,8]naphthyridine (2): To a solution of 2-amino-5,7-dimethyl[1,8]naphthyridine (**1**) (10 g, 58 mmol) in ethanol (125 ml) was added slowly 10 g (108 mmol) of chloroacetone and 5 g (59 mmol) of sodium bicarbonate. The reaction mixture was stirred under reflux for 9 h. After cooling the mixture to room temperature, the solution was evaporated, basified (Na_2CO_3) and extracted with methylene chloride. The organic layers were dried over anhydrous sodium sulfate and removed *in vacuo*. The residue was chromatographed on neutral alumina eluting with methylene chloride to give **2** (3.05 g, 25 %) ; mp 149-151°C (recrystallization solvent : ethyl acetate/hexane, 2/8) ; ir (KBr) ν_{max} 1620, 1432, 1166; ^1H -nmr (CDCl_3) δ 2.50 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.00 (s, 1H, H-7), 7.42 (AB system, 2H, $J = 9.5$ Hz, H-4, 5), 8.15 (s, 1H, H-1) ; ^{13}C -nmr (CDCl_3) δ 14.37 (CH_3 -2), 18.70 (CH_3 -6), 24.67 (CH_3 -8), 108.85 (C-1), 114.45 (C-5a), 115.79 (C-4), 120.23 (C-5), 121.83 (C-7), 141.82 (C-2), 142.64 (C-3a), 144.20 (C-9a), 146.05 (C-6), 157.85 (C-8) ; ms (m/z , relative intensity) 211 (M^+ , 100), 106 (8), 39 (11) ; *Anal.* Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3$: C, 73.93 ; H, 6.16 ; N, 19.91. Found : C, 73.90 ; H, 6.15 ; N, 19.95.

General procedure for the preparation of aldehydes (4,5) : Phosphoryl chloride (4 g, 26 mmol) was added to a cooled (0°C) *N,N*-dimethylformamide (1.9 g, 26 mmol). The appropriate naphthyridine (**2** or **3**) (10 mmol) was then added portionwise and the mixture heated at 100°C for 17 h for derivative (**2**) or 1 h for derivative (**3**). After being cooled with ice-water, the solution was basified (Na_2CO_3) and

extracted with methylene chloride. The organic layers were dried over anhydrous sodium sulfate and removed *in vacuo*. Aldehydes (**4** and **5**) were purified by recrystallization from chloroform for compound (**4**) or by column chromatography on silica gel (eluent : methylene chloride/ethanol, 98/2, v/v) for compound (**5**).

1-Formyl-2,6,8-trimethylimidazo[1,2-*a*][1,8]naphthyridine (4) : 52 % yield ; mp >260°C ; ir (KBr) ν_{\max} 1640, 1334, 794 ; $^1\text{H-nmr}$ (CDCl_3) δ 2.65 (s, 6H, 2xCH₃), 2.80 (s, 3H, CH₃), 7.20 (s, 1H, H-7), 7.55 (d, 1H, $J = 9$ Hz, H-5), 7.75 (d, 1H, $J = 9$ Hz, H-4), 11.55 (s, 1H, CHO) ; $^{13}\text{C-nmr}$ (CDCl_3) δ 16.74 (CH₃-2), 19.09 (CH₃-6), 24.74 (CH₃-8), 116.11 (C-4), 116.72 (C-1), 122.88 (C-5), 124.37 (C-7), 127.44 (C-5a), 144.97 (C-2), 146.09 (C-3a), 147.05 (C-9a), 153.06 (C-6), 159.57 (C-8), 185.77 (CHO) ; ms (m/z , relative intensity) 239 (M^+ , 22), 211 (100), 77 (24), 75 (24), 51 (18), 39 (15) ; *Anal.* Calcd for C₁₄H₁₃N₃O : C, 70.29 ; H, 5.44 ; N, 17.57. Found : C, 70.12 ; H, 5.46 ; N, 17.61.

6,8-Dimethyl-1-formyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridine (5) : 98 % yield ; mp 201-203°C (recrystallization solvent : ether) ; ir (KBr) ν_{\max} 1660, 1345, 775 ; $^1\text{H-nmr}$ (CDCl_3) δ 2.67 (s, 3H, CH₃), 2.69 (s, 3H, CH₃), 7.20 (s, 1H, H-7), 7.49 (m, 3H, Ph), 7.63 (d, 1H, $J = 9.5$ Hz, H-5), 7.81 (d, 1H, $J = 9.5$ Hz, H-4), 8.10 (m, 2H, Ph), 10.78 (s, 1H, CHO) ; $^{13}\text{C-nmr}$ (CDCl_3) δ 19.10 (CH₃-6), 24.72 (CH₃-8), 116.23 (C-5a), 116.54 (C-4), 123.04 (C-5), 124.69 (C-7), 126.25 (C-1), 127.95 (2C-Ph), 129.45 (C-Ph), 130.26 (2C-Ph), 133.35 (C-2), 145.19 (C-Ph), 146.43 (C-3a), 147.04 (C-9a), 159.55 (C-6), 159.61 (C-8), 183.98 (CHO) ; ms (m/z , relative intensity) 301 (M^+ , 42), 273 (100), 142 (10), 39 (12) ; *Anal.* Calcd for C₁₉H₁₅N₃O : C, 75.75 ; H, 4.98 ; N, 13.95. Found : C, 75.56 ; H, 4.99 ; N, 13.99.

General procedure for the preparation of azidovinyl compounds (6,7) : Ethyl azidoacetate (4 g, 31 mmol) was added dropwise at -30°C to a stirred solution containing sodium (0.8 g, 34.8 mmol) in dry ethanol (25 ml). To this solution was added a mixture of the corresponding aldehyde (**4** or **5**) (2.67 mmol) in dry ethanol (25 ml). The reaction mixture was returned to room temperature and stirred for 2 h (for compound (**4**)) or 18 h (for **5**). After this it was poured into aqueous saturated ammonium chloride (100 ml) and extracted with methylene chloride. The organic layers were dried (Na_2SO_4) and removed under reduced pressure. The residue was purified by neutral alumina column to afford the corresponding azide (**6,7**).

Ethyl α -azido- β -(2,6,8-trimethylimidazo[1,2-*a*][1,8]naphthyridin-1-yl)propenoate (6) :

Elution with methylene chloride gave a solid mixture (0.2 g) of **6** with aldehyde (**4**) in a ratio of 65/35. Due to the complexity of the mixture only ^1H -nmr and ms signals are listed. Ir (KBr) ν_{max} 2050 (N_3) ; ^1H -nmr (CDCl_3) δ 1.40 (t, 3H, $J = 7$ Hz, CH_3), 2.50 (m, 9H, $3\times\text{CH}_3$), 4.40 (q, 2H, $J = 7$ Hz, CH_2), 7.34 (s, 1H, H-7), 7.51 (d, 1H, $J = 9.5$ Hz, H-4), 7.80 (d, 1H, $J = 9.5$ Hz, H-5), 8.28 (s, 1H, H- β) ; ms (m/z , relative intensity) 324 (M^+ , 19), 248 (100), 224 (53), 123 (12).

Ethyl α -azido- β -(6,8-dimethyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridin-1-yl)propenoate (7) :

Elution with methylene chloride/hexane (6/4, v/v) afforded **7** as a paste. Yield : 22 % ; ir (KBr) ν_{max} 2050, 1700, 1360 ; ^1H -nmr (CDCl_3) δ 1.38 (t, 3H, $J = 7$ Hz, CH_3), 2.45 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.40 (q, 2H, $J = 7$ Hz, CH_2), 6.95 (s, 1H, H-7), 7.40 (m, 1H, Ph), 7.48 (m, 4H, Ph, H-4,5), 7.75 (m, 2H, Ph), 8.58 (s, 1H, H- β) ; ^{13}C -nmr (CDCl_3) δ 14.32 (CH_3), 18.39 (CH_3 -6), 24.41 (CH_3 -8), 61.37 (CH_2), 115.52 (C-5a), 116.82 (C-4), 118.64 (C- α), 118.86 (C-5), 121.44 (C-7 or C- β), 122.48 (C- β or C-7), 124.57 (C-1), 127.51 (2C-Ph), 128.04 (C-Ph), 128.18 (2C-Ph), 135.56 (C-2), 144.72 (C-Ph), 145.02 (C-3a, C-9a), 145.91 (C-6), 157.61 (C-8), 163.24 (CO) ; *Anal.* Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_6\text{O}_2$: C, 66.99 ; H, 4.85 ; N, 20.39. Found : C, 66.82 ; H, 4.83 ; N, 20.45.

General procedure for the preparation of iminophosphoranes (8,13) : To a solution of the azidovinyls (**6**, **7**) (2.4 mmol) in dry methylene chloride (10 ml) was added dropwise at 0°C a solution of triphenylphosphine (1 g, 3.8 mmol) in the same solvent (20 ml). The reaction mixture was stirred at room temperature for 4-18 h and the solvent was removed *in vacuo*. The residue was purified by neutral alumina column chromatography eluting by methylene chloride to give the corresponding iminophosphoranes (**8**, **13**).

Ethyl α -triphenylphosphoranylideneamino- β -(6,8-dimethyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridin-1-yl)propenoate (8) :

Yield : 50 % ; mp $> 260^\circ\text{C}$ (recrystallization solvent : hexane) ; ir (KBr) ν_{max} 1690, 1430, 1215, 690 ; ^1H -nmr (CDCl_3) δ 1.22 (t, 3H, $J = 7$ Hz, CH_3), 2.57 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.07 (q, 2H, $J = 7$ Hz, CH_2), 7.03 (s, 1H, H-7), 7.32 (m, 20H, Ph), 7.50 (AB system, 2H, $J = 9.5$ Hz, H-4,5), 8.08 (d, 1H, $J = 7$ Hz, H- β) ; ^{13}C -nmr (CDCl_3) δ 14.45 (CH_3), 19.14 (CH_3 -6), 24.57 (CH_3 -8), 60.76 (CH_2), 110.68 ($^3J_{\text{P-C}} = 21$ Hz, C- β), 115.94 (C-5a), 116.83 (C-4), 120.17 (C-5), 121.19 (C-7), 123.70 (C-1), 126.60 (2C-Ph), 127.70 ($^3J_{\text{P-C}} = 12$ Hz, 6C-Ph), 127.80 (C-Ph), 130.45 (2C-Ph), 132.51 ($^2J_{\text{P-C}} = 10$ Hz, 6C-Ph), 133.57 (C-2), 136.41 ($^2J_{\text{P-C}} = 6$ Hz,

C- α), 142.20 (C-Ph), 133.25 ($^1J_{P-C} = 100$ Hz, 3C-Ph), 144.72 (C-3a), 145.95 (C-9a), 156.14 (C-8, C-6), 168.03 ($^3J_{P-C} = 7$ Hz, CO) ; ms (m/z, relative intensity) 646 (M⁺, 1), 183 (16), 108 (18), 73 (14), 60 (100) ; *Anal.* Calcd for C₄₁H₃₅N₄O₂P : C, 76.16 ; H, 5.42 ; N, 8.67. Found C, 76.42 ; H, 5.40 ; N, 8.68.

Ethyl α -triphenylphosphoranylideneamino- β -(6,8-dimethylimidazo[1,2-a][1,8]naphthyridin-2-yl)propenoate (13) : Yield : 87 % ; mp >260°C (recrystallization solvent : ether) ; ir (KBr) ν_{\max} 1690, 1590, 1395, 1205, 700 ; 1H -nmr (CDCl₃) δ 1.10 (t, 3H, $J = 7$ Hz, CH₃), 2.55 (s, 3H, CH₃), 2.60 (s, 3H, CH₃), 3.90 (q, 2H, $J = 7$ Hz, CH₂), 7.01 (s, 1H, H-7), 7.14 (d, 1H, $J = 8$ Hz, H- β), 7.45 (m, 11H, H-4, Ph), 7.55 (m, 6H, H-5, Ph), 9.35 (s, 1H, H-1) ; ^{13}C -nmr (CDCl₃) δ 14.05 (CH₃), 18.71 (CH₃-6), 24.79 (CH₃-8), 60.75 (CH₂), 111.59 ($^3J_{P-C} = 21$ Hz, C- β), 112.63 (C-1), 114.59 (C-5a), 115.96 (C-4), 119.96 (C-5), 121.58 (C-7), 128.30 ($^3J_{P-C} = 12$ Hz, 6C-Ph), 130.83 ($^4J_{P-C} = 2$ Hz, 3C-Ph), 132.42 ($^2J_{P-C} = 9.5$ Hz, 6C-Ph), 133.28 ($^1J_{P-C} = 105$ Hz, 3C-Ph), 137.05 ($^2J_{P-C} = 7$ Hz, C- α), 142.92 (C-2), 143.04 (C-3a), 143.69 (C-9a), 145.70 (C-6), 157.34 (C-8), 167.42 ($^3J_{P-C} = 8$ Hz, CO) ; ms (m/z, relative intensity) 570 (M⁺, 26), 286 (100), 235 (92), 183 (80), 108 (44) ; *Anal.* Calcd for C₃₅H₃₁N₄O₂P : C, 73.68 ; H, 5.44 ; N, 9.82. Found : C, 73.75 ; H, 5.42 ; N, 9.84

General procedure for the preparation of imidazodiones (10a,b) : A solution of the iminophosphorane (8) (0.8 g, 1.2 mmol) in toluene (10 ml) was added dropwise at 0°C to a stirred solution containing ethyl (or phenyl) isocyanate (1.4 mmol) in toluene (10 ml). The solution was stirred at 0°C for 30 min, then at room temperature for 3 h (and at 50°C for 6 h with ethyl isocyanate). The solvent was removed *in vacuo* and the crude carbodiimide was chromatographed on neutral alumina eluting with methylene chloride to yield the desired products 10a,b.

(Z)-5-[(6,8-Dimethyl-2-phenylimidazo[1,2-a][1,8]naphthyridin-1-yl)methylidene]-3-ethylimidazolidine-2,4-dione (10a) : 39 % yield ; mp > 260°C (recrystallization solvent : methylene chloride) ; ir (KBr) ν_{\max} 1760, 1720, 1670, 1400, 1200, 725 ; 1H -nmr (CDCl₃) δ 1.55 (t, 3H, $J = 7$ Hz, CH₃), 2.66 (s, 3H, CH₃), 2.75 (s, 3H, CH₃), 3.65 (q, 2H, $J = 7$ Hz, CH₂), 6.60 (s, 1H, NH), 7.20 (s, 1H, H-7), 7.34 (m, 3H, Ph), 7.65 (AB system, 2H, $J = 9$ Hz, H-4,5), 7.73 (m, 2H, Ph), 8.59 (s, 1H, H- β) ; ^{13}C -nmr (CDCl₃) δ 13.68 (CH₃), 19.13 (CH₃-6), 24.82 (CH₃-8), 33.78 (CH₂), 103.72 (C- β), 116.10 (C-5a), 116.47 (C-4), 119.04 (C- α), 122.36 (C-7), 122.82 (C-5), 125.60 (C-1), 127.59 (2C-Ph), 128.75 (C-Ph), 128.78 (2C-Ph), 133.33 (C-2), 144.18 (C-Ph), 145.37 (C-3a), 146.13 (C-9a), 146.47

(C-6), 153.82 (C-8), 157.98 (CO), 163.74 (CO) ; ms (m/z, relative intensity) 411 (M⁺, 100), 341 (24), 312 (65), 284 (28), 157 (23) ; *Anal.* Calcd for C₂₄H₂₁N₅O₂ : C, 70.07 ; H, 5.11 ; N, 17.03. Found : C, 70.12 ; H, 5.10 ; N, 17.06.

(Z)-5-[(6,8-Dimethyl-2-phenylimidazo[1,2-a][1,8]naphthyridin-1-yl)methylidene]-3-phenylimidazolidine-2,6-dione (10b) : 58 % yield ; mp > 260°C (recrystallization solvent : methylene chloride) ; ir (KBr) ν_{\max} 1760, 1720, 1400, 725 ; ¹H-nmr (DMSO-d₆) δ 2.60 (s, 3H, CH₃), 2.71 (s, 3H, CH₃), 7.39 (s, 1H, H-7), 7.52 (m, 8H, Ph), 7.78 (s, 1H, H- β), 7.79 (AB system, 2H, *J* = 9.5 Hz, H-4,5), 7.96 (m, 2H, Ph), 8.45 (s, 1H, NH) ; ¹³C-nmr (DMSO-d₆) δ 18.53 (CH₃-6), 24.10 (CH₃-8), 102.62 (C- β), 115.49 (C-5a), 116.29 (C-4), 116.88 (C- α), 122.15 (C-7), 122.86 (C-5), 126.61 (2C-Ph), 127.76 (2C-Ph), 127.80 (C-Ph), 127.87 (C-1), 127.94 (C-Ph), 128.26 (2C-Ph), 128.87 (2C-Ph), 131.71 (C-Ph), 134.10 (C-2), 143.54 (C-Ph), 144.53 (C-3a), 145.30 (C-9a), 146.61 (C-6), 153.82 (C-8), 156.86 (CO), 162.32 (CO) ; ms (m/z, relative intensity) 459 (M⁺, 46), 339 (41), 324 (56), 312 (84), 284 (47), 157 (62), 142 (42), 91 (49), 77 (100) ; *Anal.* Calcd for C₂₈H₂₁N₅O₂ : C, 73.20 ; H, 4.58 ; N, 15.25. Found : C, 73.33 ; H, 4.58 ; N, 15.23.

Other method. To a solution of the iminophosphorane (**8**) (0.68 g, 1.05 mmol) in 1,6-dibromohexane (20 ml) was added 1.5 mmol of the appropriate isocyanate. After stirring at reflux for 6 h, the solvent was removed *in vacuo* and the crude product precipitated in methylene chloride. By filtration, we obtained the (Z)-imidazolidine-2,6-diones (**10a,b**) in 12 % and 17 % yields, respectively.

General procedure for the preparation of methoxyimidazoles (11a,b) : A solution of the crude carbodiimide prepared by the above method was immediately flash chromatographed on neutral alumina eluting with methanol to yield the desired products (**11a,b**).

(Z)-3,5-Dihydro-5-[(6,8-dimethyl-2-phenylimidazo[1,2-a][1,8]naphthyridin-1-yl)methylidene]-3-ethyl-2-methoxy-4H-imidazol-4-one (11a) : 47 % yield ; mp 185-187°C (recrystallization solvent : ether) ; ir (KBr) ν_{\max} 1720, 1652, 1590, 1475, 1270, 700 ; ¹H-nmr (CDCl₃) δ 1.17 (t, 3H, *J* = 7 Hz, CH₃), 2.65 (s, 3H, CH₃), 2.71 (s, 3H, CH₃), 3.44 (s, 3H, OMe), 3.52 (q, 2H, *J* = 7 Hz, CH₂), 7.13 (s, 1H, H-7), 7.28 (t, 1H, *J* = 7 Hz, Ph), 7.32 (m, 2H, Ph), 7.63 (AB system, 2H, *J* = 9.5 Hz, H-4,5), 7.75 (m, 2H, Ph), 8.74 (s, 1H, H- β) ; ¹³C-nmr (CDCl₃) δ 14.15 (CH₃-6), 19.08 (CH₃-8), 24.80 (CH₃), 34.39 (CH₂), 56.05 (OMe), 114.69 (C- β), 115.87 (C-5a), 116.60 (C-4), 120.46 (C- α), 122.08 (C-7, C-5), 127.00 (C-Ph), 127.84 (2C-Ph), 128.69 (2C-Ph), 136.65 (C-1), 136.97

(C-2), 145.53 (C-Ph), 145.82 (C-3a), 146.12 (C-9a), 147.34 (C-6), 157.89 (C-8), 161.49 (CO), 168.44 (C-OMe); ms (*m/z*, relative intensity) 425 (M^+ , 100), 410 (56), 311 (42), 284 (36), 58 (30); *Anal.* Calcd for $C_{25}H_{23}N_5O_2$: C, 70.59; H, 5.41; N, 16.47. Found: C, 70.41; H, 5.43; N, 16.52.

(Z)-3,5-Dihydro-5-[(6,8-dimethyl-2-phenylimidazo[1,2-*a*][1,8]naphthyridin-1-yl)methylidene]-2-methoxy-3-phenyl-4*H*-imidazol-4-one (11b): 42 % yield; mp 185-187°C (recrystallization solvent: ether); ir (KBr) ν_{\max} 1720, 1640, 1570, 1430, 750; 1H -nmr ($CDCl_3$) δ 2.67 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.45 (s, 3H, OMe), 7.12 (s, 1H, H-7), 7.35 (m, 8H, Ph), 7.61 (AB system, 2H, $J = 9$ Hz, H-4,5), 7.81 (m, 2H, Ph), 8.91 (s, 1H, H- β); ^{13}C -nmr ($CDCl_3$) δ 19.13 (CH_3 -6), 24.83 (CH_3 -8), 56.43 (OMe), 115.86 (C- β), 116.02 (C-5a), 116.70 (C-4), 120.49 (C- α), 122.22 (C-7), 122.32 (C-5), 125.77 (2C-Ph), 127.18 (C-Ph), 127.78 (C-Ph), 127.96 (2C-Ph), 128.76 (2C-Ph), 129.08 (2C-Ph), 132.30 (C-1), 135.98 (C-Ph), 136.68 (C-2), 144.87 (C-Ph), 145.58 (C-3a), 145.99 (C-9a), 146.18 (C-6), 158.03 (C-8), 159.95 (CO), 167.53 (C-OMe); ms (*m/z*, relative intensity) 473 (M^+ , 44), 324 (100), 284 (32), 177 (20), 163 (27), 142 (25); *Anal.* Calcd for $C_{29}H_{23}N_5O_2$: C, 73.57; H, 4.86; N, 14.80. Found: C, 73.75; H, 4.87; N, 14.81.

Other method. A solution of the crude carbodiimide (0.210 g) in methanol (20 ml) was heated with stirring at reflux for 8 h. Then the solvent was removed *in vacuo* and the crude product was chromatographed on neutral alumina with methylene chloride as eluent to give a solid mixture of (*Z*)- and (*E*)-isomers of the methoxyimidazoles (**11a,b**) which could be identified by nmr spectroscopy.

(E) isomer 11a: 1H -nmr ($CDCl_3$) δ 1.03 (t, 3H, $J = 7$ Hz, CH_3), 2.60 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 3.35 (q, 2H, $J = 7$ Hz, CH_2), 4.16 (s, 3H, OMe), 7.09 (s, 1H, H-7), 7.29 (t, 1H, $J = 7$ Hz, Ph), 7.33 (t, 2H, $J = 7$ Hz, Ph), 7.61 (AB system, 2H, $J = 9$ Hz, H-4,5), 7.86 (d, 2H, $J = 7$ Hz, Ph), 7.98 (s, 1H, H- β); ^{13}C -nmr ($CDCl_3$) δ 13.82 (CH_3 -6), 19.22 (CH_3 -8), 24.85 (CH_3), 33.96 (CH_2), 66.25 (OMe), 116.88 (C-4), 118.12 (C- β), 121.70 (C-5), 121.98 (C-7), 127.48 (C-Ph), 128.15 (2C-Ph), 128.37 (2C-Ph), quaternary carbons not observed.

(E) isomer 11b: 1H -nmr ($CDCl_3$) δ 2.58 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.17 (s, 3H, OMe), 7.08 (s, 1H, H-7), 7.29 (t, 1H, $J = 7$ Hz, Ph), 7.35 (m, 5H, Ph), 7.42 (t, 2H, $J = 7$ Hz, Ph), 7.61 (AB system, 2H, $J = 9$ Hz, H-4, 5), 7.89 (m, 2H, Ph), 8.06 (s, 1H, H- β); ^{13}C -nmr ($CDCl_3$) δ 19.07 (CH_3 -6), 24.76 (CH_3 -8), 56.38 (OMe), 116.83 (C-4), 118.82 (C- β), 121.95 (C-5), 122.08 (C-7), 125.94 (2C-Ph),

127.21 (C-Ph), 127.58 (2C-Ph), 128.34 (2C-Ph), 128.47 (C-Ph), 128.99 (2C-Ph), quaternary carbons not observed.

Reactions of iminophosphorane (13) with ethyl and phenyl isocyanates. To a cooled (0°C) solution of the iminophosphorane (13) (0.6 g, 1.05 mmol) in dry toluene (100 ml) was added a solution of ethyl or phenyl isocyanate (1.56 mmol) in the same solvent (10 ml). The mixture was stirred at room temperature for 1 h then heated at reflux during 2 h. After cooling, the solvent was removed under reduced pressure and the residual material washed with methylene chloride to remove phosphine oxide. Chromatography on neutral alumina column eluting with methylene chloride yielded compounds (14 a,b and 15).

A. From the reaction of iminophosphorane (13) and ethyl isocyanate, the elution yielded 2,4-dimethyl-10-ethoxycarbonyl-8-ethylaminopyrimidino[1',6':1,5]imidazo[1,2-a][1,8]naphthyridinium betaine (14a): 63 % yield; mp 245-247°C (recrystallization solvent: methylene chloride); ir (KBr) ν_{\max} 1690, 1640, 1570, 1240; $^1\text{H-nmr}$ (CDCl_3) δ 1.45 (m, 6H, 2xCH₃), 2.81 (s, 3H, CH₃), 2.83 (s, 3H, CH₃), 3.82 (q, 2H, $J = 7$ Hz, CH₂), 4.44 (q, 2H, $J = 7$ Hz, CH₂), 7.30 (s, 1H, H-3), 7.45 (s, 1H, H-11), 8.09 (d, 1H, $J = 10$ Hz, H-5), 8.57 (s, 1H, H-12), 9.80 (d, 1H, $J = 10$ Hz, H-6); $^1\text{H-nmr}$ (MeOD + DCl) δ 1.65 (m, 6H, 2xCH₃), 3.04 (s, 3H, CH₃-2), 3.08 (s, 3H, CH₃-4), 4.03 (q, 2H, $J = 7$ Hz, N-CH₂), 4.65 (q, 2H, $J = 7$ Hz, O-CH₂), 7.97 (s, 1H, H-3), 8.13 (s, 1H, H-11), 8.98 (AB system, 2H, $J = 9.5$ Hz, H-5,6), 9.58 (s, 1H, H-12); $^{13}\text{C-nmr}$ (MeOD + DCl) δ 14.92 (2xCH₃), 19.04 (CH₃-4), 25.47 (CH₃-2), 39.52 (NCH₂), 63.57 (O-CH₂), 104.76 (C-11), 108.57 (C-12), 111.91 (C-6), 119.88 (C-4), 128.09 (C-3), 131.43 (C-5), 134.05 (C-6a), 134.52 (C-11a), 141.24 (C-10), 141.90 (C-13a), 146.19 (C-8), 150.71 (C-4a), 165.23 (C-2, CO); ms (m/z , relative intensity) 363 (M⁺, 76), 334 (89), 263 (50), 235 (100), 222 (27), 184 (27); *Anal.* Calcd for C₂₀H₂₁N₅O₂: C, 66.12; H, 5.79; N, 19.28. Found: C, 66.27; H, 5.77; N, 19.24.

B. From the reaction of iminophosphorane (13) and phenyl isocyanate, the first elution yielded 2,4-dimethyl-10-ethoxycarbonyl-8-phenylaminopyrimidino[1',6':1,5]imidazo[1,2-a][1,8]naphthyridinium betaine (14b): 56 % Yield; mp > 260°C (recrystallization solvent: methylene chloride); ir (KBr) ν_{\max} 1700, 1625, 1540, 765; $^1\text{H-nmr}$ (CDCl_3) δ 1.45 (t, 3H, $J = 7$ Hz, CH₃), 2.78 (s, 3H, CH₃), 2.79 (s, 3H, CH₃), 4.38 (q, 2H, $J = 7$ Hz, CH₂), 6.98 (t, 1H, $J = 7$ Hz, Ph), 7.06 (s, 1H, H-3), 7.34 (t, 2H, $J = 7$ Hz, Ph), 7.42 (s, 1H, H-11), 7.88 (d, 2H, $J = 7$ Hz, Ph), 8.03 (d, 1H, $J = 9.5$ Hz, H-5), 8.62

(s, 1H, H-12), 9.90 (d, 1H, $J = 9.5$ Hz, H-6) ; ^{13}C -nmr (CDCl_3) δ 14.34, 18.92, 25.14, 61.57, 90.64, 114.91, 121.51, 123.69, 124.38 (2C), 125.42, 128.48 (3C), quaternary carbons not observed ; ms (m/z , relative intensity) 411 (M^+ , 100), 382 (54), 338 (63), 236 (76), 77 (27) ; *Anal.* Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_2$: C, 70.07 ; H, 5.11 ; N, 17.03. Found : C, 70.28 ; H, 5.09 ; N, 17.08. Further elution yielded 2,4-dimethyl-10-ethoxycarbonyl-8-hydroxypyrimidino[1',6':1,5]imidazo[1,2-*a*][1,8]naphthyridinium betaine (**15**) : 21 % Yield ; mp 189-191°C (recrystallization solvent : methylene chloride) ; ir (KBr) ν_{max} 1710, 1670, 1575, 1230, 770 ; ^1H -nmr (CDCl_3) δ 1.45 (t, 3H, $J = 7$ Hz, CH_3), 2.85 (s, 6H, $2\times\text{CH}_3$), 4.45 (q, 2H, $J = 7$ Hz, CH_2), 7.45 (s, 1H, H-3), 7.50 (s, 1H, H-11), 8.15 (d, 1H, $J = 10$ Hz, H-5), 8.77 (s, 1H, H-12), 9.30 (d, 1H, $J = 10$ Hz, H-6) ; ^{13}C -nmr (CDCl_3) δ 14.37 (CH_3), 18.93 (CH_3 -4), 25.11 (CH_3 -2), 61.89 (CH_2), 94.89 (C-11), 102.82 (C-12), 112.92 (C-6), 117.03 (C-4a), 125.24 (C-5), 125.82 (C-3), 133.09 (C-10), 135.98 (C-11a), 139.61 (C-6a), 146.32 (C-13a), 147.89 (C-4), 149.80 (C-2), 161.98 (C-8), 165.85 (CO) ; ms (m/z , relative intensity) 336 (M^+ , 11), 264 (63), 236 (100), 142 (12) ; *Anal.* Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_3$: C, 64.29 ; H, 4.76 ; N, 16.67. Found : C, 64.51 ; H, 4.75 ; N, 16.69.

REFERENCES

1. R. Kazlauskas, P.T. Murphy, R.J. Quinn, and R.J. Wells, *Tetrahedron Lett.*, 1977, 61.
2. K. H. Hollenbeak and F.J. Schmitz, *Lloydia*, 1977, 40, 479.
3. J.T. Baker and R.J. Wells in "Natural Products as Medicinal Agents", Eds by J.L. Beal and E. Reinhardt, Hippokrates Verlag, Stuttgart, 1981, 299.
4. C.V.R. Sastry, B. Ram, M. Jogibhukta, V.S.H. Krishnan, A.N. Singh, J.G. Reddy, S.C. Chaturvedi, P.S. Rao, and D.R. Shridhar, *Indian J. Chem., Sect. B*, 1989, 28, 52.
5. P. Djura and D.J. Faulkner, *J. Org. Chem.*, 1980, 45, 735.
6. (a) P. Molina, P.M. Fresneda, and P. Almendros, *Tetrahedron Lett.*, 1992, 33, 4491. (b) P. Molina, P. Almendros, and P.M. Fresneda, *Tetrahedron*, 1994, 50, 2241.
7. (a) J.C. Chermann, J. Gruet, L. Montagnier, F. Wendling, P. Tambourin, M. Perrin, F. Pochon, C. Ducrocq, C. Rivalle, and E. Bisagni, *C. R. Hebd. Séances Acad. Sci. Paris*, 1977, 285, ser. D, 945. (b) F. Marsais, P. Pineau, F. Nivolliers, M. Mallet, A. Turck, A. Godard, and G. Queguiner, *J. Org. Chem.*, 1992, 57, 565.

8. A. Gueiffier, Y. Blache, H. Viols, J.P. Chapat, O. Chavignon, J.C. Teulade, G. Dauphin, J.C. Debouzy, and J.L. Chabard, *J. Heterocycl. Chem.*, 1992, **29**, 283.
9. J. Bernstein, B. Stearns, E. Shaw, and W.A. Lott, *J. Am. Chem. Soc.*, 1947, **69**, 1151.
10. O. Chavignon, J.C. Teulade, M. Madesclaire, A. Gueiffier, Y. Blache, H. Viols, J.P. Chapat, and G. Dauphin, *J. Heterocycl. Chem.*, 1992, **29**, 691.
11. O. Chavignon, J.C. Teulade, D. Roche, M. Madesclaire, Y. Blache, A. Gueiffier, J.L. Chabard, and G. Dauphin, *J. Org. Chem.*, 1994, **59**, 6413.
12. P. Molina, A. Arques, A. Alias, M.V. Vinader, M.C. Foces-Foces, and F. Hernandez-Cano, *Tetrahedron*, 1992, **48**, 3091.
13. G. Guella, I. Mancini, H. Zibrowius, and F. Pietra, *Helv. Chim. Acta*, 1988, **71**, 773.
14. M.A. Abdel-Rahman, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 510.

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