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IMINOPHOSPHORANE-MEDIATED SYNTHESIS OF FUSED CARBAZOLES. A FACILE ONE-POT PREPARATION OF 7H-PYRIDO [4,3-c]CARBAZOLE AND 10H-PYRIDO[3,4-b]CARBAZOLE DERIVATIVES.

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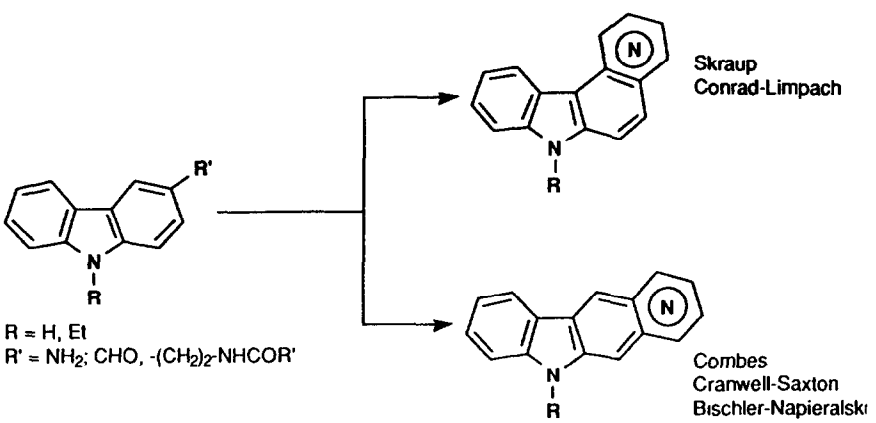
Abstract.- The aza Wittig-type reaction of iminophosphorane **3**, ethyl α-[(triphenylphosphoranylidene) amino]-β-[3-(9-methyl)carbazolyl)acrylate with isocyanates leads to the corresponding pyrido[4,3-c]carbazoles **5**. Similarly, iminophosphorane **8** undergoes pyrido annelation by reaction with isocyanates to give the isomeric 10H-pyrido [3,4-b]carbazoles (isoellipticines) **10**

Ellipticine, 9-methoxyellipticine, olivacine and other 6H-pyrido[4,3-b]carbazoles have received much attention because they exhibit broad spectrum antitumor activity in a variety of experimental model both in vitro and in vivo[1]. The size and the shape of the 6H-pyridocarbazole ring lead to an almost perfect overlapping of the aromatic ring with that of a DNA base pair[2]. As a consequence synthetic activity involving this ring system has been vigorous and unabated[3,4]. However, in contrast to synthetic and structure-activity studies focused on 6H-pyridocarbazoles very little attention has been directed towards the isomeric pyridocarbazoles.

In the series of 7H-pyridocarbazoles, dimeric bisintercalators endowed as antitumor agents[5], among these, ditercalinium (NSC 366241), have been recently introduced in Phase 1 clinical trials. Methyl substitution on well-defined positions (6 or 7) of 7H-Pyrido[4,3-c]carbazoles appears to be a crucial parameter for the DNA complex formation and antitumor activity[6]. Nevertheless, the preparation of new derivatives of this ring system able to intercalate into DNA remains an attractive way to look for new antitumor drugs. However, very few methods are available for the synthesis of 7H-pyrido[4,3-c] carbazoles. All of them are based on the oxidative photocyclization of an appropriate 1-(2-indolyl)-2-(4-pyridyl)ethylene derivative[7] (C-type synthesis according to Sainsbury's classification[3a]).

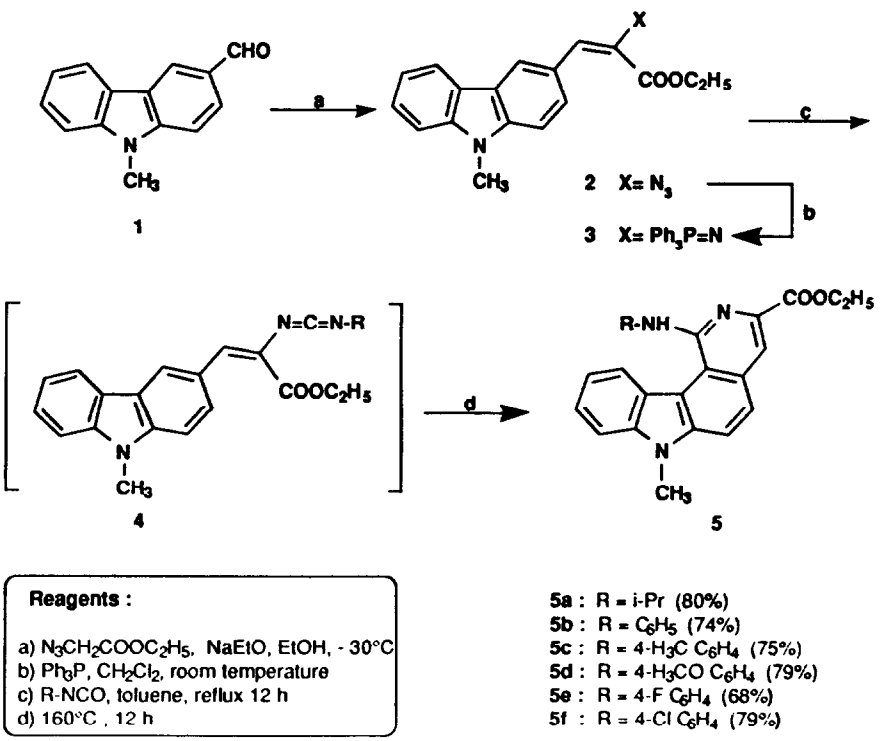
In the same manner, very little attention has been focused on the isomeric 10H-pyrido-[3,4-b] carbazoles (isoellipticines). So far the only reported[8] synthesis of isoellipticines is based on the regioselective acylation of 3-lithio-1-(phenylsulphonyl)indole with cinchomeronic anhydride; however, it has also been reported that Diels-Alder reaction of pyrano [3,4-b] indoles[9] or 4H-furo[3,4-b]indoles[10] with 3,4-pyridine leads to a mixture of ellipticine and isoellipticine.

In the course of our studies directed toward the synthesis of fused heterocycles based on heterocyclization reaction of carbodiimides we have developed the so-called tandem aza-Wittig/electrocyclization strategy for the synthesis of pyridines[11] and isoquinoline derivatives[12]. As a further extension of the above methodology we would like now to report a fundamentally new approach to the synthesis of 7H-pyrido[4,3-c] and 10H-pyrido[3,4-b]carbazoles by thermally induced 6π-electrocyclization of conjugated carbodiimides. Our approach is centered on the aza-Wittig type reaction of vinyl iminophosphoranes with isocyanates or isothiocyanates to give a 2-aza-1,3,5-hexatriene moiety containing a carbodiimide function at one end. Pyrido annelation is achieved by electrocyclic ring closure followed by [1,3] proton shift. In this context, it is worth noticing that various pyrido annelations involving 3-substituted carbazoles have been reported, but no clear pattern emerges from an examination of the direction of closure in which there are alternatives. Thus, 9-ethyl-3-aminocarbazole underwent the Skraup[13] and Conrad-Limpach[14] reaction, closure occurring at C-4 giving the angular isomer; similarly this compound reacted with formaldehyde and α- or β-naphthol by C-C bonding at carbazole C-4 producing the angular isomer[15]. On the other hand, Combes reaction of 9-ethyl-3-aminocarbazole with pentan-2,4-dione led to the linear isomer[13], and Bischler-Napieralski cyclization of amides derived from carbazole with the side chain at C-3 apparently occurred at C-2 to give the linear isomer[16]. The acid catalyzed cyclization of aldimines derived from 3-formylcarbazoles and 2,2-diethoxyethylamine has been much used for the preparation of pyridocarbazoles (Cranwell-Saxton reaction) and in only two examples a small amount of the angular isomer in addition to the linear pyridocarbazole was isolated[17].



Results.- The 3-formyl-9-methylcarbazole **1** was condensed with ethyl azidoacetate in the presence of sodium ethoxide at -30°C to give the ethyl α-azido–β-(3-carbazolyl) acrylate **2** as crystalline solid in 75% yield. The preparation of the key intermediate iminophosphorane **3** was accomplished easily by Staudinger's reaction of **2** with triphenylphosphine in dichloromethane at room temperature. The IR spectrum of **3** shows a carbonyl absorption band at 1681cm $^{-1}$, and the ^{1}H-NMR spectrum displays among

other signals a doublet at δ=7.05 ppm ($^4J_{P-H}$=7Hz), corresponding to the β-proton. Mass spectrum shows the expected molecular ion peak in low intensity, the base peak appearing at m/z 69. An aza-Wittig type reaction of the iminophosphorane **3** with aromatic or aliphatic isocyanates in dry refluxing toluene for 12 h gave the corresponding carbodiimides **4** which either could be isolated as viscous oils by means of short-column chromatography or used without purification for the next step. After an unsuccessful attempt to cyclize **4** to the desired pyridocarbazole using relatively mild thermal conditions (reflux, toluene, 4 days), we examined strong thermal conditions. Thus, heating of **4** at 160°C for 12 h under nitrogen afforded **5** in 68-80% yields after recrystallization in complete regioselective fashion. The isomeric linear pyridocarbazoles could not be detected by thin layer chomatography or ^{13}C-NMR analysis of the crude product.

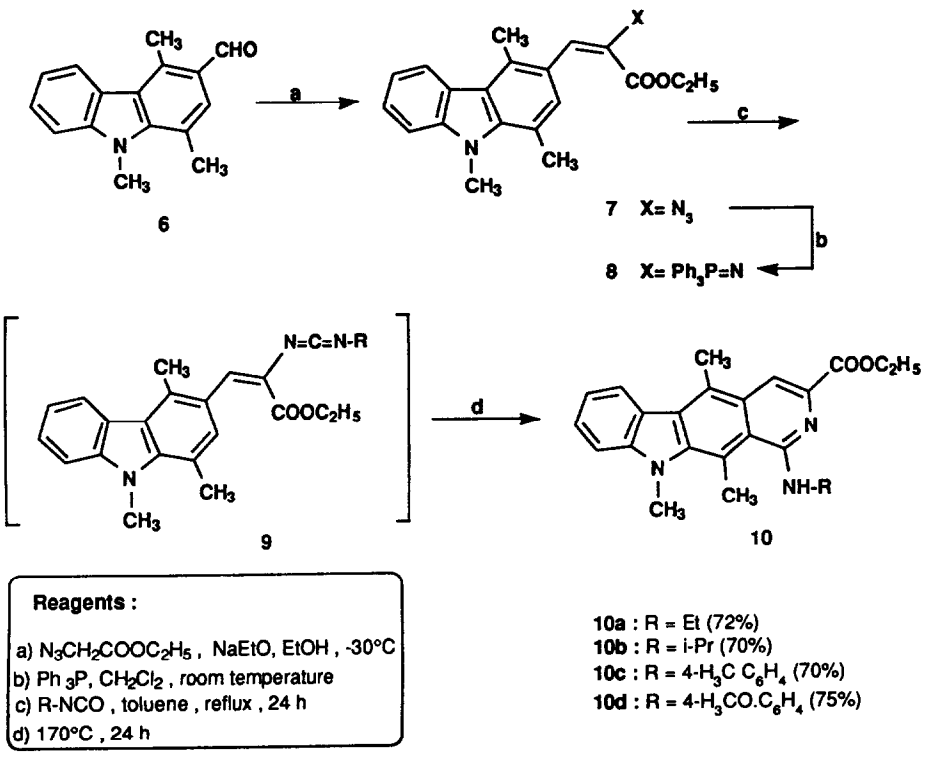


Scheme I

The IR spectra of the 7H pyrido [4,3c] carbazoles **5** show absorption bands due to the NH stretching at 3392-3342 cm $^{-1}$ and to the carbonyl group at 1714-1704 cm $^{-1}$. In the ^{1}H-NMR spectrum the protons 5-H and 6-H appear as a doublets at δ=7 55-7.66 ppm and δ=7.47-7 64 ppm respectively, whereas the 4-H proton appears as a singlet at δ=7.83-7 95 ppm. The ^{1}H-NMR spectrum suggest an exocyclic N-H for

5; e.g. in (**5a** R=i-Pr), the exocyclic methine proton appears as a multiplet and the amino proton as a doublet. Salient features of the ^{13}C-NMR spectrum are given in table I. The mass spectrum shows the expected molecular ion peaks as the base peak except for compounds **5a** and **5f** and the fragmentation pattern is in agreement with the proposed structure. The conversion **4**→**5** involves regioselective electrocyclic ring-closure followed by a [1,3] proton shift to 7H-pyrido[4,3-c]carbazoles **5**.

This approach has also shown to be useful for the preparation of the otherwise not readily available 10H-pyrido[3,4-b]carbazoles **10** (isoellipticines) bearing an amino group in the 1-position and an ethoxycarbonyl group in the 3-position, under neutral conditions. The key intermediate iminophosphorane **8** was easily prepared from 3-formyl-1,4,9-trimethylcarbazole **6** by standard chemistry: condensation with ethyl azidoacetate afforded **7** in 80% yield, and further treatment with triphenylphosphine yielded **8** in 80%. Iminophosphorane **8** reacted with aromatic or aliphatic isocyanates in dry refluxing toluene for 24 h to give the corresponding carbodiimides **9** which underwent at 170°C for 24 h ring closure to give the corresponding 10H-pyrido [3,4-b]carbazoles **10** in 70-75% yields.

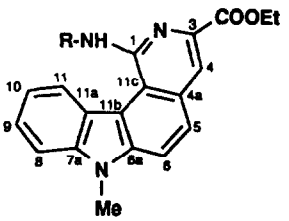


Scheme II

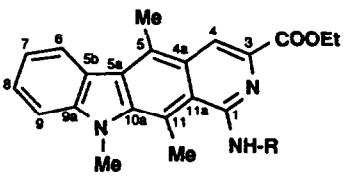
It is worth nothing that electrocyclization of carbodiimides **9** requires thermal conditions stronger than electrocyclization of carbodiimides **4**. In other words, carbazole derivatives bearing in the 3-position a C=C conjugated carbodiimide moiety as side chain undergo ring-closure onto 4-position (angular isomer) much easier than 2-position (linear isomer). This fact could explain the regioselectivity observed in the ring closure of **4** to give **5**. The identity of compounds **10** was accomplished by 2D-NMR, HCCOR, and DEPT experiments. In the ^{1}H-NMR spectrum the 4-H proton appears as a singlet at δ=8.07-8.32 ppm. Salient features of the ^{13}C-NMR spectra are given in table I.

The present study demostrated that tandem aza Wittig/electrocyclic ring-closure strategy afford a new entry to a variety of substituted fused carbazoles. Our approach is simple and direct and leds from readily available carbazoles to the key intermediates **3** and **8** in a few steps in an overall yields of 61% and 64% respectively. The subsequent cyclization and aromatization which have been described previously, take place in good yields (68-80%). Further, the approach offers an entry to a number of substituted deri vatives of isoellipticine with a high degree of functionality and a opportunity exists to exploit the amino and the ethoxycarbonyl functions to manipulate the pyridocarbazoles at a later stage.

Table I. ^{13}C Chemical Shifts (ppm) for Carbon Atoms in the Heteroaromatic Ring of Several 7H-Pyrido [4,3-c] carbazoles (**5**) and 10H-Pyrido [3,4-b] carbazoles (**10**).



5



10

Carbon Atoms	Compound			
	5a	**5c**	**10b**	**10c**
C_1	153.65 (d) J=0.5	150.0 (s)	154.95 (d) J=1.2	151.97 (m)
C_3	137.61 (s)	137.0 (s)	135.43 (m)	135.1 (m)
C_4	114.62 (dt) J=166.2, J=4.5	116.7 (dt) J=162.0, J=4.3	111.0 (d) J=165	113.80 (d) J=165
C_{4a}	131.94 (dt) J=7.2, J=2.5	132.3 (m)	130.28 (m)	127.91 (m)

C_5	126.41 (ddd)	126.5 (ddd)	127.63 (m)	127.48 (m)
	J=162.9, J=5.2	J=162.6, J=5.3		
	J=1.0	J= 1.0		
C_{5a}	—	—	125.86 (m)	126.35 (m)
C_{5b}	—	—	123.17 (t)	123.17 (t)
			J=6.4	J=6.5
C_6	113.28 (d)	113.8 (d)	123.93 (dd)	124.1 (dd)
	J=161.5	J=162	J=160.4, J=8	J=159.8, J=7.5
C_{6a}	140.34 (m)[a]	140.4 (m)[a]	—	—
C_7	—	—	123.18 (dd)	119.86 (dd)
			J=161.2, J=7.2	J=161.4, J=7
C_{7a}	140.42 (m)[a]	140.7 (m)[a]	—	—
C_8	109.26 (dd)	109.60 (dd)	127.14 (dd)	127.43 (dd)
	J=160.4 , J=8.2	J=160.6, J=8.1	J=161, J=7.7	J=160.2, J=7
C_9	125.0 (dd)	125.20 (dd)	108.94 (dd)	109.02 (dd)
	J=161, J=8.2	J=161, J=8.1	J=160.4, J=8	J=160.5,J=7.
C_{9a}	—	—	145.84 (m)	145.62 (m)
C_{10}	118.92 (dt)	119.30 (dt)	—	—
	J=156.2, J=4	J=160, J=3.9		
C_{10a}	—	—	143.51 (m)	143.73 (m)
C_{11}	124.39 (d)	123.70 (d)	111.5 (m)	111.1 (m)
	J=161	J=160		
C_{11a}	121.45 (d)	121.30 (m)	120.53 (m)	121.34 (m)
	J=9.4			
C_{11b}	113.25 (m)	122.60 (m)	—	—
C_{11c}	115.70 (t)	116.1 (t)	—	—
	J=9.4	J=5.8		

[a] Interchangeables.

Experimental:

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions on a Nicolet FT-5DX Spectrophotometer. ^1H and ^{13}C NMR

spectra were recorded on a Brucker AC-200, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Two-dimensional spectra and DEPT experiments were recorded using standard conditions. Electron-impact mass spectra were carried out on a Hewlett-Packard 5993C spectrometer at an ionization potential of 70 eV. Microanalysis were performed on a Perkin-Elmer 240C instrument.

Materials. 3-Formyl-9-methylcarbazole[18] **1** and 3-formyl-1,4,9-trimethylcarbazole[19] **6** were prepared as described in the literature.

Preparation of Ethyl α–Azido-β (3-carbazolyl)acrylates (2 and 7).

Ethyl azidoacetate (5.16g, 40 mmol) and a solution of the appropriate 3-formylcarbazole **1** or **6** (10 mmol) in dry ethanol (10 ml) were added dropwise under nitrogen at -30 °C to a well-stirred solution containing sodium (0.92g) in dry ethanol (50 ml). The reaction mixture was stirred at -20 °C for 6 h, poured into cold water (100 ml) and then extracted with diethyl ether (for **2**) or dichloromethane (for **7**) (3x30 ml). The combined organic layers were washed with water (3x10 ml), dried over anhydrous sodium sulfate, and filtered. Concentration to dryness yielded a crude material which was recrystallized from the appropriate solvent.

Ethyl α-Azido-β-[3-(9-methyl)carbazolyl]acrylate (2). (75%), m.p. 101-103°C dec.(yellow prisms from diethyl ether/n-hexane 1:1). (Found: C, 67.23; H, 4.87; N, 17.65.$C_{18}H_{16}N_4O$ requires: C, 67.49; H, 5.03; N, 17.49); i.r. (Nujol) 2107(azide) and 1695(COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.39 (t, 3H, J=7.16Hz), 3.69 (s, 3H, CH_9-N), 4.34 (q, 2H, J=7.16Hz), 7.07 (s, 1H, $H_β$), 7.23 (d, 1H, J=9.0Hz, H_1), 7.25 (t, 1H, J=8.0Hz, H_6), 7.30 (d, 1H, J=9.0Hz, H_8), 7.45 (dd, 1H, J=8.15, 0.8Hz, H_7), 7.88 (dd, 1H, J=8.7, 1.0Hz, H_2), 8.15 (d, 1H, J=7.9Hz, H_5), 8.50 (s, 1H, H_4); ^{13}C n.m.r. δ ($CDCl_3$): 14.2 (CH_3-CH_2O), 29.0 (CH_3N), 61.9 (CH_3-CH_2O), 108.2 (C_1), 108.6 (C_8), 119.5 (C6), 120.4 (C5), 122.5 ($C_α$), 122.7 (C_{4a}), 122.8 (C_{4b}), 123.13 (C_4), 124.2 (C_3), 126.0 (C_7), 127.1 ($C_β$), 128.8 (C_2), 141.3 (C_{9a}), 141.4 (C_{8a}), 163.9 (CO); m/z (%): 320 (M^+, 2), 218 (100).

Ethyl α-Azido-β-[3-(1,4,9-trimethyl)carbazolyl]acrylate (7). (80%), m.p. 111-113°C dec. (yellow prisms from diethyl ether/dichloromethane/n-hexane 1:1:2). (Found: C, 69.21; H 5.62; N , 15.88. $C_{20}H_{20}N_4O_2$ requires: C, 68.95; H, 5.79; N, 16.08); i.r. (Nujol) 2108 (azide) and 1692 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.43 (t, 3H, J=7.15Hz), 2.80 (s, 6H, CH_3-C_1 and CH_3-C_4), 4.02 (s,3H, CH_3-N), 4.39 (q, 2H, J=7.15Hz), 7.23 (t, 1H, J=8.8Hz, H_6), 7.35 (d, 1H, J=7.9Hz, H_8), 7.43 (s, 1H, $H_β$), 7.46 (t, 1H, J=7.6Hz, H_7), 7.79 (s, 1H, H_2), 8.18 (d, 1H, J=7.9Hz, H_5); ^{13}C n.m.r. δ ($CDCl_3$): 14.3 (CH_3-CH_2O), 16.80 (CH_3-C_1), 20.6 (CH_3-C_4), 32.2 (CH_3N), 62.0 (CH_3-CH_2O), 108.5 (C_8), 117.3 (C_1), 119.3 (C_6), 122.2 ($C_α$), 122.8 (C_5), 122.9 (C_{4b}), 123.6 (C_{4a}), 123.9 (C_3), 124.9 ($C_β$), 125.1 (C_7), 130.2 (C_2), 131.9 (C_4), 140.0 (C_{9a}), 141.8 (C_{8a}), 163.9 (CO); m/z (%): 348 (M^+, 2), 274 (100).

General Procedure for the preparation of Ethyl α-[(Triphenylphosphoranylidene) amino]-β-(3-carbazolyl)acrylate, (3 and 8). To a solution of triphenylphosphine (1.05g, 4 mmol) in dry dichloromethane (10ml) was added dropwise under nitrogen at 0°C a solution of the appropriate ethyl α-azido-β-(3-carbazolyl)propanoate **2** or **7** (4 mmol) in the same solvent (10 ml). The reaction mixture was stirred at room temperature for 12 h, and the solvent was removed under reduced pressure at 25°C, the residual material was recrystallized from benzene/n-hexane (1:1).

Ethyl α-[(Triphenylphosphoranylidene)amino]-β-[3-(9-methyl)carbazolyl]acrylate (3). (82%), m.p. 168-170°C (yellow prisms). (Found: C, 78.09; H, 5.42; N, 4.87. $C_{36}H_{31}N_2O_2P$ requires: C, 77.96; H, 5.63; N, 5.05); i.r. (Nujol) 1681, 1157, 1108 and 1039 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.04 (t, 3H, J=7.2Hz), 3.81 (s, 3H, CH_3N), 3.92 (q, 2H, J=7.2Hz), 7.05 (d, 1H, J_{H-P}=7Hz, H_β), 7.15 (dt, 1H, J=7.8, 1.0Hz, H_6), 7.30 (d, 1H, J=8.6Hz, H_1), 7.35 (d, 1H, J=9.5Hz, H_8), 7.40-7.60 (m, 10H), 7.70-7.90 (m, 7H), 7.95 (dd, 1H, J=8.6, 1.5Hz, H_2), 9.43(s, 1H, H_4); ^{13}C n.m.r. δ ($CDCl_3$): 14.0 (CH_3-CH_2O), 28.9 (CH_3N), 60.5 (CH_3-CH_2O), 107.5 (C_1), 108.2 (C_8), 118.1 (d, $^3J_{P-C}$=19.6Hz, C_β), 118.3 (C_6), 120.5 (C_5), 121.0 (C_4), 122.6 (C_{4a}), 123.2 (C_{4b}), 125.1 (C_7), 128.1 (d, $^3J_{P-C}$=12.2Hz, C_m), 128.6 (C_2), 129.5 (d, $^4J_{P-C}$=2.5Hz, C_3), 130.7 (d, $^4J_{P-C}$=2.5Hz, C_p), 132.4 (d, $^2J_{P-C}$=9.8Hz, C_o), 133.4 (d, $^1J_{P-C}$=103Hz, C_i), 134.0 (d, $^2J_{P-C}$=6.8Hz, C_α), 133.7 (C_{9a}), 141.2 (C_{8a}), 168.1 (d, $^3J_{P-C}$=6.9Hz, CO); m/z (%): 554 (M^+, 5), 69 (100).

Ethyl α-[(Triphenylphosphoranylidene)amino]-β-[3-(1,4,9-trimethyl) carbazolyl] acrylate (8): (80%), m.p. 179-181°C (yellow prisms). (Found: C, 78.59; H, 5.89; N, 4.59. $C_{38}H_{35}N_2O_2P$ requires: C, 78.33; H, 6.05; N, 4.81); i.r. (Nujol) 1695, 1112, 1107 and 1048 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.02 (t, 3H, J=7.13Hz), 2.66 (s, 3H, CH_3-C_4), 2.86 (s, 3H, CH_3-C_1), 3.91 (q, 2H, J=7.13Hz), 4.03 (s, 3H, CH_3N), 7.19 (t, 1H, J=7.3Hz, H_6), 7.22 (d, 1H, J_{H-P}=6Hz, H_β), 7.30-7.40 (m, 11H), 7.60-7.80 (m, 6H), 8.24 (d, 1H, J=7.8Hz, H_5), 8.69 (s, 1H, H_2); ^{13}C n.m.r. δ ($CDCl_3$): 14.1 (CH_3-CH_2O), 16.7 (CH_3-C_1), 20.3 (CH_3-C_4), 32.2 (CH_3N), 60.5 (CH_3-CH_2O), 108.1 (C_8), 115.4 (d, $^3J_{P-C}$=19.5Hz, C_β), 116.1 (C_1), 118.5 (C_6), 122.1 (C_{4b}), 122.8 (C_5), 124.2 (C_{4a}), 124.3 (C_7), 127.8 (C_3), 128 (d, $^3J_{P-C}$=12Hz, C_m), 129.8 (C_4), 130.7 (d, $^4J_{P-C}$=2.94Hz, C_p), 131.2 (C_2), 132.5 (d, $^2J_{P-C}$=9.4Hz, C_o), 133.3 (d, $^1J_{P-C}$=103Hz, (C_i),134.3 (d, $^2J_{P-C}$=6Hz, C_α), 138.5 (C_{9a}), 141.8 (C_{8a}), 168.6 (d, $^3J_{P-C}$=6.2Hz, CO); m/z (%): 582 (m^+, 25), 183 (100).

General Procedure for the preparation of Ethyl 1-amino-7-methyl-7H-pyrido[4,3-c]carbazole-3-carboxylates (5) and Ethyl 1-amino-5,10,11-trimethyl-10H-pyrido[3,4-b]carbazole-3-carboxylates (10).

To a solution of iminophosphorane **3** or **8** (1 mmol) in dry toluene (30 ml), was added dropwise under nitrogen at 0°C the appropriate isocyanate. The reaction mixture was stirred at refflux for 12 h (for compounds **5**) or 24 h (for compounds **10**). After cooling, the solvent was removed and the formed

carbodiimide **4** or **9** was heated under nitrogen in an oil bath at 160°C for 12 h (for compounds **5**) or at 170°C for 24 h (for compounds **10**). The crude product was chromatographed on a silica gel column, eluting with dichloromethane to afford **5** or **10** as crystalline solids.

5a: (80%), m.p. 133-135°C (orange prisms from ethanol/ethyl acetate); (Found: C, 72.90; H, 6.32; N, 11.53. $C_{22}H_{23}N_3O_2$ requires: C, 73.11; H, 6.41; N, 11.63); i.r. (Nujol) 3347 (NH) and 1713 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.41 (d, 6H, J=6.5Hz), 1.50 (t, 3H, J=7.1Hz), 3.73 (s, 3H, CH_3N), 4.47 (q, 2H, J=7.1Hz), 4.74 (m, 1H, J=6.5Hz), 5.54 (d, 1H, J=7.4Hz, NH), 7.29 (dd, 1H, J=6.4, 1.5Hz, H_{10}), 7.37 (d, 1H, J=8.3Hz, H_8), 7.42 (t, 1H, J=6.5Hz, H_9), 7.47 (d, 1H, j=8.8Hz, H_6), 7.57 (d, 1H, J=8.8Hz, H_5), 7.83 (s, 1H, H_4), 8.73 (d, 1H, J=8.2Hz, H_{11}); ^{13}C n.m.r. δ ($CDCl_3$): 14.29 (*CH_3*-CH_2O), 22.8 (*$(CH_3)_2$*CH), 29.0 (CH_3N), 43.1 ($(CH_3)_2$*CH*), 60.72 (CH_3-*CH_2*), 109.26 (C_8), 113.25 (C_{11b}), 113.28 (C_6), 114.62 (C_4), 115.70 (C_{11c}), 118.92 (C_{10}), 121.45 (C_{11a}), 124.39 (C_{11}), 125.0 (C_9), 126.41 (C_5), 131.94 (C_{4a}), 137.61 (C_3), 140.34 (C_{6a}), 140.42 (C_{7a}), 153.65 (C_1), 166.6 (CO); m/z (%): 361 (M^+, 18), 257 (100).

5b: (74%), m.p. 192-193°C (yellow prisms from ethanol/ethyl acetate). (Found: C, 76.21; H, 5.48; N, 10.43. $C_{25}H_{21}N_3O_2$ requires: C, 75.93; H, 5.35; N, 10.63); i.r. (Nujol) 3392 (NH), 1711 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.53 (t, 3H, J=7.2Hz), 3.78 (s, 3H, CH_3N), 4.47 (q, 2H, J=7.2Hz), 7.08 (t, 1H, J=7.4Hz, H_p), 7.25 (dd, 1H, J=8.2, 2Hz, H_{10}), 7.54 (d, 1H, J=8.8Hz, H_6), 7.40-7.51 (m, 4H, H_8+H_9+2H_m), 7.58 (d, 1H, J=8.8Hz, H_5), 7.68 (s, 1H, NH), 7.94 (s, 1H, H_4), 8.04 (d, 2H, J=7.8Hz, H_o), 8.38 (d, 1H, J=8.2Hz, H_{11}); ^{13}C δ n.m.r. ($CDCl_3$): 14.3 (*CH_3*-CH_2O), 29.2 (CH_3N), 61.0 (CH_3-*CH_2*), 109.6 (C_8), 112.6 (C_{11b}), 113.7 (C_6), 116.15 (C_{11c}), 117.0 (C_4), 118.3 (C_o), 119.9 (C_{10}), 121.3 (C_{11a}), 121.6 (C_p), 123.62 (C_{11}), 125.3 (C_9), 126.63 (C_5), 129.2 (C_m), 123.3 (C_{4a}), 136.92 (C_3), 140.13 (C_i), 140.43 (C_{6a}), 140.72 (C_{7a}), 149.92 (C_1), 166.23 (CO); m/z (%): 395 (M^+, 100), 321 (73).

5c: (75%), m.p. 198-200°C; (orange prisms from ethanol/ethyl acetate). (Found: C, 76.39; H, 5.53; N, 9.98. $C_{26}H_{23}N_3O_2$ requires: C, 76.28; H, 5.66; N, 10.26); i.r. (Nujol) 3364 (NH) and 1709 (COOEt) cm-1; ^1H n.m.r. δ ($CDCl_3$): 1.50 (t, 3H, J=7.1Hz), 2.36 (s, 3H, CH_3Ar), 3.66 (s, 3H, CH_3N), 4.42 (q, 2H, J=7.1Hz), 7.24 (d, 2H, J=8.8Hz, H_m), 7.25 (m, 1H, H_{10}), 7.42 (d, 1H, J=8Hz, H_8), 7.44 (t, 1H, j=7.8Hz, H_9), 7.51 (d, 1H, J=9Hz, H_6), 7.56 (d, 1H, J=9Hz, H_5), 7.64 (s, 1H, NH), 7.91 (s, 1H, H_4), 7.93 (d, 2H, J=8,8Hz, H_o), 8,39 (d, 1H, J=8.2Hz, H_{11}); ^{13}C n.m.r. δ ($CDCl_3$): 14.32 (*CH_3*-CH_2O), 20.70 (CH_3Ar), 29.40 (CH_3N), 60.91 (CH_3-*CH_2*O), 109.60(C_8), 112.60 (C_{11b}), 113.80 (C_6), 116.1 (C_{11c}), 116.70 (C_4), 118.30 (C_o), 119.30 (C_{10}), 121.30 (C_{11a}), 123.70 (C_{11}), 125.20 (C_9), 126.50 (C_5), 129.47 (C_m), 131.0 (C_p), 132.30 (C_{4a}), 137.0 (C_3), 137.60 (C_i), 140.40 (C_{6a}),140.70 (C_{7a}), 150.0 (C_1), 166.32 (CO); m/z (%): 409 (M^+, 100), 335 (37).

5d: (79%), m.p. 201-202°C (yellow prisms from ethanol/ethyl acetate). (Found: C, 74.16; H, 5.63; N, 10.13. $C_{26}H_{23}N_3O_3$ requires: C, 74.30; H, 5.45; N, 9.88); i.r. (Nujol) 3358 (NH) and 1714 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.51 (t, 3H, J=7.1Hz), 3.77 (s, 3H, CH_3N), 3.84 (s, 3H, CH_3OAr), 4.45 (q, 2H, J=7.1Hz),

6.98 (d, 2H, J=8.6Hz, H_m),7.25 (td, 1H, J=8.4 2Hz, H_{10}), 7.41 (d, 1H, J=8.3Hz, H_8), 7.44 (t, 1H, J=8Hz, H_9), 7.51 (d, 1H, J=8.6Hz, H_6), 7.55 (d, 1H, J=8.6Hz, H_5), 7.57 (s, 1H, NH), 7.89 (s, 1H, H_4), 7.95 (d, 2H, J=8.9Hz, H_o), 8.38 (d, 1H, J=8.2Hz, H_{11}); ^{13}C n.m.r. δ ($CDCl_3$): 14.32 (CH_3-CH_2O), 29.13 (CH_3N), 55.5 (CH_3OAr), 60.9 (CH_3-CH_2O), 109.60 (C_8), 112.60 (C_{11b}), 113.70 (C_6), 114.30 (C_m), 115.80 (C_{11c}), 116.50 (C_4), 119.60 (C_o), 119.80 (C_{10}), 121.30 (C_{11a}), 123.60 (C_{11}), 125.20 (C_9), 126.50 (C_5), 132.20 (C_i), 133.70 (C_{4a}), 137.0 (C_3), 150.10 (C_1), 154.60 (C_p), 166.20 (CO); m/z (%): 425 (M^+, 100), 351 (23).

5e: (68%), m.p. 219-220°C (orange prisms from ethanol/ethyl acetato). (Found: C, 72.51; H, 5.07; N, 10.33. $C_{25}H_{20}FN_3O_2$ requires: C, 72.63; H, 4.88; N, 10.16); i.r. (Nujol) 3344 (NH) and 1704 (COOEt) cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$): 1.50 (t, 3H, J=7Hz), 3.86 (s, 3H, CH_3-N), 4.44 (q, 2H, J=7Hz), 7.01 (dd, 2H, J=9, 8.7Hz, H_m), 7.25 (m, 1H, H_{10}), 7.51 (s, 1H, NH), 7.58 (m, 2H, H_8+H_9), 7.64 (d, 1H, J=9.3Hz, H_6), 7.66 (d, 1H, J=9.3Hz,H_5), 7.90 (dd, 2H, J=9, 4.8Hz, H_o), 7.95 (s, 1H, H_4), 8.35 (d, 1H, J=8.2Hz, H_{11});^{13}C n.m.r. δ ($CDCl_3$): 14.2 (CH_3-CH_2O), 29.2 (CH_3N), 60.1 (CH_3-CH_2O), 109.7 (C_8), 112.9 (C_{11b}), 114.3 (C_6), 155.5 (C_m), 116.0 (C_{11c}), 117.2 (C_4), 119.7(C_o), 120.0 (C_{10}), 121.2 (C_{11a}), 123.6 (C_{11}), 125.5 (C_9), 126.6 (C_5), 132.3 (C_{4a}), 136.0 (C_i), 136.1 (C_3),140.5 (C_{6a}) 140.8 (C_{7a}), 149.8 (C_1), 158.0 (C_p), 165.7 (C_o); m/z (%): 413 (M^+, 100), 339 (93).

5f: (79%), m.p. 249-250°C dec. (yellow plates from dichloromethane); (Found: C, 70.06; H, 4.48; N, 9.93. $C_{25}H_{20}ClN_3O_2$ requires: C, 69.85; H, 4.69; N, 9.77); i.r. (Nujol) 3342 (NH) and 1707 (COOEt) cm-^{1}; ^{1}H n.m.r. δ (DMSO-d_6+TFA): 1.43 (t, 3H, J=7.1Hz), 4.12 (s, 3H, CH_3N), 4.42 (q, 2H, J=7.1Hz), 7.29 (t, 1H, J=7.8Hz, H_{10}), 7.46 (d, 2H, J=8.8Hz, H_m), 7.59 (t, 1H, J=7.8Hz, H_9), 7.83 (d, 1H, J=8.6Hz, H_8), 7.95 (d, 2H, J=8.8Hz, H_o), 8.15 (d, 1H, J=8.8Hz, H_6), 8.30 (s, 1H, H_4), 8.31 (d, 1H, J=8.8Hz, H_5), 8.45 (d, 1H, J=8.4Hz, H_{11}); ^{13}C n.m.r. δ (DMSO-d_6+TFA): 14.3 (CH_3-CH_2O), 29.17 (CH_3N), 60.95 (CH_3-CH_2O), 110.5 (C_8), 115.5 (C_{11b}), 116.0 (C_{11c}), 118.5 (C_6), 191.1 (C_4), 120.5 (C_{11a}), 120.8 (C_{10}), 123.5 (C_o), 124.0 (C_{11}), 126.34 (C_i), 126.5 (C_5), 127.4 (C_9), 130.5 (C_m), 131.9 (C_p), 132.3 (C_{4a}), 134.3 (C_3), 141.4 (C_{6a}), 142.1 (C_{7a}), 150.2 (C_1), 161.9 (CO); m/z (%): 431 (M+2, 8), 429 (M^+, 31), 320 (34), 319 (100).

10a: (72%), m.p. 170-172°C (orange prisms from ethanol); (Found: C, 73.47; H, 6.89; N, 10.95. $C_{23}H_{25}N_3O_2$ requires: C, 73.57; H, 6.71; N, 11.9); i.r. (Nujol) 3434 (NH) and 1717 (COOEt) cm^{-1}; ^{1}H n.m.r δ ($CDCl_3$): 1.38 (t, 3H, J=7.2Hz), 1.47 (t, 3H, J=7.1Hz), 2.75 (s,3H, CH_3-C_{11}), 2.90 (s, 3H, CH_3-C_5), 3.71 (q, 2H, J=7.2Hz), 3.78 (s, 3H, CH_3N), 4.46 (q, 2H, J=7.1Hz), 4.98 (s br, 1H, NH), 7.19 (t, 1H, J=7.5Hz, H_7), 7.22 (d, 1H, J=8.6Hz, H_9), 7.46 (t, 1H, J=7.5Hz, H_8), 8.07 (s, 1H, H_4), 8.08 (d, 1H, J=7.8Hz, H_6); ^{13}C n.m.r. δ ($CDCl_3$): 14.37 (CH_3-CH_2O), 14.69 (CH_3-CH_2NH), 12.57 (CH_3-C_{11}), 19.59 (CH_3-C_5), 34.17 (CH_3N), 37.1 (CH_3-CH_2-NH), 60.86 (CH_3-CH_2O), 108.69 (C_9), 110.87 (C_{11}), 111.17 (C_4), 119.46 (C_7), 120.40 (C_{11a}), 122.98 (C_{5b}), 123.79 (C_6), 125.44 (C_{5a}), 126.91 (C_8), 127.37 (C_5), 130.05 (C_{4a}), 135.93 (C_3), 143.07 (C_{10a}), 145.19 (C_{9a}), 155.76 (C_1), 167.06 (CO); m/z (%): 375 (M^+, 84), 258 (100).

10b: (70%), m.p. 182-184°C (orange prisms from ethanol/ethyl acetate); (Found: C, 73.88; H, 7.17; N, 10.61. $C_{24}H_{27}N_3O_2$ requires: C, 74.01; H, 6.99; N, 10.79); i.r. (Nujol) 3417 (NH) and 1721 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.38 (d, 6H, J=6.4Hz), 1.47 (t, 3H, J=7.2Hz), 2.92 (s, 3H, CH_3-C_{11}), 3.01 (s, 3H, CH_3-C_5), 3.90 (s, 3H, CH_3N), 4.46 (q, 2H, J=7.2Hz), 4.65 (m, 1H), 4.90 (d, 1H, J=7Hz, NH), 7.24 (t, 1H, J=7.2Hz, H_7), 7.31 (d, 1H, J=8.2Hz, H_9), 7.51 (dd, 1H, J=7.2, 0.6Hz, H_8), 8.15 (s, 1H, H_4), 8.20 (d, 1H, J=7.9Hz, H_6); ^{13}C n.m.r. δ ($CDCl_3$): 14.39 (*CH_3*-CH_2O), 15.49 (CH_3-C_{11}), 19.91 (CH_3-C_5), 22.85 (*$(CH_3)_2$*CH), 34.39 (CH_3N), 43.58 ($(CH_3)_2$*CH*-), 60.94 (CH_3-*CH_2*O), 108.94 (C_9), 111.0 (C_4), 111.50 (C_{11}), 120.53 (C_{11a}), 123.17 (C_{5b}), 123.18 (C_7), 123.93 (C_6), 125.86 (C_{5a}), 127.14 (C_8), 127.63 (C_5), 130.28 (C_{4a}), 135.43 (C_3), 143.51 (C_{10a}), 145.84 (C_{9a}), 154.95 (C_1), 166.85 (CO); m/z (%): 389 (M^+, 33), 258 (100).

10c: (70%), m.p. 187-189°C (orange plates from ethanol/ethyl acetate/n-hexane); (Found: C, 76.65; H, 6.43; N, 9.79. $C_{28}H_{27}N_3O_2$ requires: C, 76.86; H, 6.22; N, 9.60); i.r. (Nujol) 3454 (NH) and 1718 (COOEt) cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.49 (t, 3H, J=7.1Hz), 2.37 (s, 3H, CH_3Ar), 2.92 (s, 3H, CH_3-C_{11}), 2.96 (s, 3H, CH_3-C_5), 3.88 (s, 3H, CH_3N), 4.45 (q, 2H, J=7.1Hz), 7.00 (s br, 1H, NH), 7.11 (d, 2H, J=8.3Hz, H_m), 7.26 (t, 1H, J=7.5Hz, H_7), 7.32 (d, 1H, J=8Hz, H_9), 7.54 (t, 1H, J=7.5Hz, H_8), 7.58 (d, 2H, J=8.3Hz, H_o), 8.20 (d, 1H, J=7.8Hz, H_6), 8.32 (s, 1H, H_4); ^{13}C n.m.r. δ ($CDCl_3$): 14.43 (*CH_3*-CH_2O), 15.56 (CH_3-C_{11}), 19.74 (CH_3-C_5), 20.74 (CH_3Ar), 61.08 (CH_3-*CH_2*O), 109.02 (C_9), 111.1 (C_{11}), 113.80 (C_4), 118.51 (C_o), 119.86 (C_7), 121.34 (C_{11a}), 123.17 (C_{5b}), 124.14 (C_6), 126.35 (C_{5a}), 127.43 (C_8), 127.48 (C_5), 127.91 (C_{4a}), 129.32 (C_m), 131.2 (C_p), 135.1 (C_3), 138.91 (C_i), 143.73 (C_{10a}), 145.62 (C_{9a}), 151.97 (C_1), 166.78 (CO); m/z (%): 437 (M^+, 7), 347 (21), 91 (100).

10d: (75%), m.p. 191-193°C (orange prisms from dichloromethane/n-hexane); (Found: C, 73.92; H, 5.87; N, 9.43. $C_{28}H_{27}N_3O_3$ requires: C, 74.15; H, 6.00; N, 9.26); i.r. (Nujol) 3430 (NH) and 1705 (COOEt) cm^{-1} ; ^1H n.m.r. δ ($CDCl_3$): 1.49 (t, 3H, J=7.2Hz), 2.96 (s, 3H, CH_3-C_{11}), 3.00 (s, 3H, CH_3-C_5), 3.79 (s, CH_3N), 3.92 (s, 3H, CH_3OAr), 6.96 (s br, 1H, NH), 6.87 (d, 2H, J=9Hz, H_m), 7.28 (t, 1H, J=7.2Hz, H_7), 7.35(d, 1H, J=8.2Hz, H_9), 7.55 (t, 1H, J=7.2Hz, H_8), 7.62 (d, 1H, J=8.9Hz, H_o), 8.23 (d, 1H, J=7.8Hz, H_6), 8.32 (s, 1H, H_4); ^{13}C n.m.r. δ ($CDCl_3$): 14.42 (*CH_3*-CH_2O), 15.60 (CH_3-C_{11}), 19.77 (CH_3-C_5), 34.72 (CH_3N), 55.65 (CH_3OAr), 61.05 (CH_3-*CH_2*O), 109.05 (C_9), 111.1 (C_{11}), 113.57 (C_4), 119.88 (C_7), 121.26 (C_{11a}), 123.20 (C_{5b}), 124.15 (C_6), 126.36 (C_{5a}), 127.42 (C_8), 127.50 (C_5), 127.95 (C_{4a}), 134.93 (C_3), 143.76 (C_{10a}), 145.64 (C_{9a}), 152.17 (C_1), 166.73 (CO); m/z (%): 453 (M^+, 61), 379 (35), 121 (100).

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