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An Improved Synthesis of Cyclazines from 3*H*-Pyrrolizines

Volker Batroff[a], *Wilhelm Flitsch**[a], *Derek Leaver**[b], and *David Skinner*[b]

Organisch-Chemisches Institut der Universität Münster[a],
Orléans-Ring 23, D-4400 Münster, and

Department of Chemistry, University of Edinburgh[b],
West Mains Road, Edinburgh EH9 3JJ (Scotland)

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The reaction of 3*H*-pyrrolizines **3** with vinamidinium salts **4** provides a new and generally applicable route to [2.2.3]cyclazines **5**. Pyrrolizinefulvenes are intermediates of this reaction as shown using **3f** as an example. – Cyclopenta[*h*][2.2.4]cyclazines **11** were prepared from the hitherto unknown 3*H*-pyrrolizines **3b,c,d** and the pyrrolizine esters **3e,f** with the cyclopentadiene iminium salt **10** under conditions which have been described previously. Additional evidence for a close similarity between cyclazines **11** and the corresponding azulenes has been obtained from the UV spectra of **11**.

Eine verbesserte Synthese von Cyclazinen aus 3*H*-Pyrrolizinen

Die Umsetzung von 3*H*-Pyrrolizinen **3** mit Vinamidiniumsalzen **4** bietet einen neuen, allgemein anwendbaren Zugang zu [2.2.3]Cyclazinen **5**. Am Beispiel von **3f** wurde gezeigt, daß Pyrrolizinfulvene Intermediäre dieser Reaktion sind. – Cyclopenta[*h*][2.2.4]cyclazine **11** wurden auf einem schon früher beschriebenen Wege aus den bisher unbekannten 3*H*-Pyrrolizinen **3b,c,d** und den Pyrrolizinestern **3e,f** durch Umsetzung mit dem Cyclopentadieniminiumsalz **10** erhalten. Ihre UV-Spektren zeigen zusätzliche Hinweise auf eine enge Beziehung zwischen Cyclazinen **11** und den entsprechenden Azulenen auf.

[2.2.3]Cyclazines **5** were prepared for the first time by *Boekelheide*, who also found that cycloaddition of activated acetylenes to indolizines provides a useful route to this interesting class of

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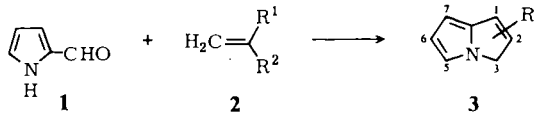
compounds[1,2]. Alternatively a reaction of pyrrolizine anions with vinamidinium salts **4** may be anticipated[3] particularly since 3*H*-pyrrolizines **3** are now well known compounds[4].

During the last years improved methods of synthesis of 3*H*-pyrrolizines **3** have been developed[5]. Several stable derivatives are now easily accessible from 2-pyrrolecarbaldehyde (**1**) and vinylphosphonates **2**. Thus ethyl 3*H*-pyrrolizine-6-carboxylate (**3g**) was obtained from 2-pyrrolecarbaldehyde (**1**) with **2e**[6].

Analogously 2-phenyl-3*H*-pyrrolizine (**3b**) was prepared using either diphenyl-(1-phenylvinyl)phosphane oxide (**2b**) (81%) or the phosphonate **2c** (45%). From a reaction of diethyl 1-(phenylsulfonyl)vinylphosphonate (**2d**) 2(6)-(phenylsulfonyl)-3*H*-pyrrolizines **3c** (85%) or **3d** (77%) were obtained depending on experimental conditions[7].

The structure of these 3*H*-pyrrolizines follows from the ^{1}H NMR spectra (Table 1).

Scheme 1

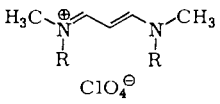


1 **2** **3**

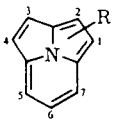
	R^1	R^2
2a	H	$PPh_3^{\oplus}\ Br^{\ominus}$
b	Ph	$POPh_2$
c	Ph	$PO(OEt)_2$
d	SO_2Ph	$PO(OEt)_2$
e	CO_2Et	$PO(OEt)_2$

	R
3a	H
b	2-Ph
c	2-SO_2Ph
d	6-SO_2Ph

	R
3e	6-CO_2Me
f	7-CO_2Et
g	6-CO_2Et



4a: R = Me
b: R = Ph



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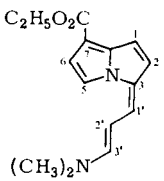
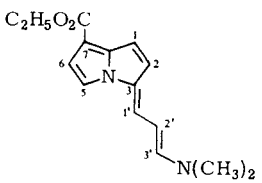
	R
5a	H
b	1-Ph
c	1-SO_2Ph

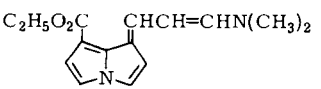
	R
5d	1-CO_2Me
e	2-CO_2Et
f	2-CO_2H



6a



6b



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The synthesis of the [2.2.3]cyclazines **5** is based on the three carbon annelation procedure of *Jutz*[8] (Scheme 1). In our preliminary communication[3] we reported that the yields of [2.2.3]cyclazines **5** obtained by reaction of vinamidinium salts **4** with the conjugate bases of 3*H*-pyrrolizines **3** are greatly increased by the presence of conjugative substituents in the pyrrolizine nucleus. We now give full details and further

examples of these reactions. However, it appears that our previous failure[9] to obtain an acceptable yield of the parent [2.2.3]cyclazine (**5a**) from 3*H*-pyrrolizine (**3a**) itself was due mainly to an insufficient period of heating. We have now increased the yield of **5a** to 46%, thus demonstrating the generality of this procedure.

The spectroscopic data of [2.2.3]cyclazines **5** which were prepared analogously from 3*H*-pyrrolizines **3** are summarized in Table 2.

Table 1. ^{1}H NMR Spectra of 3*H*-Pyrrolizines **3a – d**[a]

	Solvent	1-H	2-H	3-H	5-H	6-H	7-H
3a	CS_2	6.2	5.63	3.75	6.54	6.08	5.77
3b	[D_6]acetone	7.0	–	4.94	7.08	6.14	5.9
3c	$CDCl_3$	7.42	–	4.62	6.96	6.3	6.23
3d	$CDCl_3$	6.54	6.30	4.48	6.23	–	[b]

	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
3a	6.2	2.2	2.2	2.7	1.1	3.5
3b	–	–	–	2.7	1.0	3.5
3c	–	1.8	–	3.4	1.2	3.7
3d	6.0	3.3	1.9	–	–	–

[a] TMS as internal standard; chemical shifts are given in δ (ppm). The coupling constants are given in Hz. – [b] Lies under the aromatic protons.

Table 2. [2.2.3]Cyclazines **5b,c,e**. ^{1}H NMR Spectra[a]

	Solvent	1-H	2-H	3-H	4-H	5-H	6-H	7-H
5b	[D_6]acetone	–	7.98	7.64	7.4	8.18	7.89	8.42
5c	[D_6]acetone	–	8.12	7.81	7.53	8.20	8.06	8.46
5e	$CDCl_3$	7.79	–	7.82	7.36	7.99	7.68	8.02

	$J_{3,4}$	$J_{1,4}$	$J_{5,6}$	$J_{6,7}$
5b	4.38	–	7.8	7.8
5c	5	–	8	8
5e	4.5	0.9	7.8	7.8

[a] TMS as internal standard; chemical shifts are given in δ (ppm). The coupling constants are given in Hz.

	UV Spectra[a]
5b	430 (3.73), 244 (4.31), 212 (4.20)
5c	414 (3.97), 402 (3.95), 391 (3.86), 300 (3.94), 293 (3.94), 241 (4.37), 218 (4.20)
5e	443 (3.51), 433 (3.55), 420 (3.55), 303 (3.97), 295 (3.87), 250 (4.26)

[a] Measured in ethanol; λ_{max} [nm]; lg_{10} ε in parentheses.

When the reactions of 3*H*-pyrrolizines **3** with vinamidinium salts **4** were carried out in the presence of a base, the solutions became strongly coloured (usually red or purple) during the initial period of stirring at room temperature. This was taken as an indication of the presence of fulvenoid intermediates[8] which were slowly converted into the cyclazines **5** during a subsequent period of heating. The intermediate derived from ethyl 3*H*-pyrrolizine-7-carboxylate (**3f**) and the salt **4a**, being evidently more

Table 3. 360 MHz ^{1}H NMR Spectra[a] of the Mixture of Fulvenoid Compounds **6a** and **6b**

δ [ppm]	^3J [Hz]	^6J [Hz]	ASIS[b]	Assignment **6a**	Assignment **6b**	N.O.E. [%][c,d]
7.01	3.0		−0.10	5-H		18 (5.24)
6.88	3.0		+0.03		5-H	
6.69	3.0	0.9[e]	−0.52	6-H		
6.66	[f]		−0.42		1-H[f]	
6.66	[f]	[f]	+0.11		2-H[f]	3 (5.24)
6.63	5.3		−0.49	1-H		
6.58	12.3		+0.66	3′-H		7 (2.82)
6.56	3.0[f]	0.9	−0.52		6-H	
6.51	11.8[g,h]		+0.27		1′-H	
6.44	12.8[g,i]		+0.63		3′-H	8.5 (2.79)
6.36	5.3	0.9[e]	+0.05	2-H		
6.18	12.3		+0.26	1′-H		9 (6.36)
5.26	12.3[g,j]		+0.16		2′-H	3 (2.79)
5.22	12.3		+0.11	2′-H		5 (2.82)
						16 (7.01)
4.25			−0.06	OEt	OEt	
2.82			+0.79	NMe_2		
2.79			+0.68		NMe_2	
1.16			+0.17	OEt	OEt	

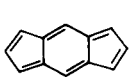
[a] Unless otherwise stated, chemical shifts and coupling constants refer to a saturated solution in $CDCl_3$. – [b] ASIS = $\delta^{CDCl_3} - \delta^{C_6H_6}$. – [c] Enhancements <3% and those of protons known to be vicinally coupled to the irradiated proton are not reported. – [d] δ value in parentheses indicates proton irradiated. – [e] Shown to be mutually coupled by double irradiation (decoupling) experiments. – [f] The resonances due to 1-H and 2-H in **6b** are coincident in $CDCl_3$ and appear as a singlet. In C_6D_6, 1-H is partially obscured by 6-H but 2-H appears as a doublet of triplets ($^3J_{1,2}$ = 5.4 Hz, $^6J_{2,6} = {}^4J_{2,1'}$ = 0.7–0.9 Hz). – [g] J refers to solution in C_6D_6. – [h] Shows additional long-range coupling ($^5J_{1,1'}$ ca. 1.4 Hz, $^4J_{2,1'} = {}^4J_{1',3'}$ = 0.5–0.7 Hz). – [i] Shows additional long-range coupling to 1′-H. – [j] Average value.

stable than other compounds of this type, remained partially unchanged even after 42 h in refluxing DMF and was then obtained as a red-brown crystalline by-product during chromatographic isolation of the desired cyclazine **5e**. More of the same substance was obtained as the sole product of a reaction at room temperature. The product was chromatographically homogeneous (TLC) but its ^{1}H NMR spectrum (Table 3) showed the presence of two isomeric compounds, the major of which was assigned the structure **6a** on the basis of the following evidence. (i) The absence of a ^{1}H resonance free from vicinal coupling eliminated the possible isomeric structure with a 1-ethoxycarbonyl group. (ii) Resonances showing low (3.0 Hz), intermediate (5.3 Hz) and high (12.3 Hz) values for the vicinal coupling constant ($^3J_{HH}$) were recognized as due to protons in the aromatic pyrrole ring (5-H and 6-H), the nonaromatic ring (1-H and 2-H) and the olefinic side-chain[10] (1′-H, 2′-H and 3′-H), respectively. (iii) The resonances due to 2-H and 6-H were recognized from their mutual splitting ($^6J_{HH}$ = 0.9 Hz), a similar long-range coupling having been reported previously[11] as a characteristic of other 3*H*-pyrrolizines. (iv) Nuclear Overhauser enhancement (N.O.E) difference spectra[12] showed the proximity of 2′-H (δ = 5.22) to 5-H (δ = 7.01) and Me_2N (δ = 2.82) and of 1′-H (δ = 6.18) to 2-H (δ = 6.36). The proton resonances due to the minor component of the mixture, though less well resolved, were similar in general features to those of the major component (Table 3). N.O.E. difference spectra showed that both

double bonds of the side chain have the *E*-configuration (2'-H close to 2-H and NMe_2) but did not yield reliable information concerning the point of attachment of the side-chain to the nucleus. A decision in favour of the stereoisomeric structure **6b** rather than **7** rests on measurements of aromatic solvent induced shifts[13] ($\Delta\delta = \delta^{CDCl_3} - \delta^{C_6D_6}$) for each of the types of protons in the two components of the mixture (Table 3). We make no attempt to explain the magnitudes and signs of these shifts in terms of solute-solvent interactions[13b] but merely draw attention to the following features. (i) In common with other molecules of the "push-pull" type[14], isomer **6a** shows negative ASIS values ($\delta = -0.49$ and -0.52), for those protons (1-H and 6-H, respectively) close to the negatively polarized group (CO_2Et) and positive values elsewhere (except for 5-H). (ii) The $\Delta\delta$ values for the protons of the minor isomer **6b** correlate well (except for 5-H) with those of the corresponding protons in **6a**; in particular, the value of $\delta = -0.42$ is readily accounted for as being due to 1-H in **6b** but is not consistent with 3-H in **7**, for which a positive $\Delta\delta$ is to be expected. (iii) The poor $\Delta\delta$ correlation for 5-H in the two isomers **6** may be attributed to the differing side-chain configurations, that of **6a** being such as to hinder the interaction of solvent molecules with 5-H.

s-Indacene (**8**) and azuleno[5,6,7-*cd*]phenalene (**9**) have been synthesized from the cyclopentadiene iminium salt **10** by reaction with the conjugate bases of cyclopentadiene ($pK_a = 15$) and phenalene ($pK_a = 19.5$), respectively[15,16]. 3*H*-Pyrrolizine (**3a**) ($pK_a = 29$)[17], though less acidic, is comparable in many ways to these acidic hydrocarbons and its reaction with the cyclopentadiene iminium salt **10** and sodium hydride, in *N,N*-dimethylformamide, gave the cyclopenta[*h*][2.2.4]cyclazine **11a** in 19% yield[18a].

Scheme 2



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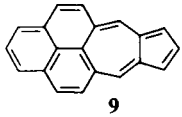

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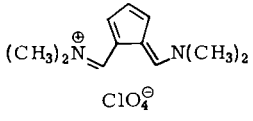

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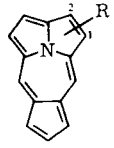


	R
11a	H
b	1-Ph
c	1-SO_2Ph
d	1-CO_2Me
e	2-CO_2Et

Derivatives **11b–e** were obtained analogously. Spectroscopic data are given in Table 4.

In previous communications we noted[18a] that conjugative electron-withdrawing substituents at the 6(8)-position of cyclopenta[*h*][2.2.4]cyclazines **11** cause a marked hypsochromic shift of the long-wavelength visible absorption band (HOMO-LUMO transition) and drew attention[18a,b] to the parallels with azulenes. We now observe further similarities to azulenes in the small bathochromic effect (32–33 nm) of 1-methoxycarbonyl and 1-phenylsulfonyl substituents (cf. 4(8)- and 6-positions of

Table 4. Cyclopenta[*h*][2.2.4]cyclazines **11b – e**. ^{1}H NMR Spectra[a]

	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H
11b	–	b)	b)	b)	8.88	b)	b)	b)	8.73
11c	–	7.93	7.45 – 7.5	7.68	8.74	7.92	8.10	8.01	9.55
11d	–	7.76	7.30	7.49	8.54	7.84	7.97	7.84	9.58
11e	8.03	–	7.62	7.61	8.61	7.81	7.89	7.83	8.67

	$J_{1,4}$	$J_{3,4}$	$J_{6,7}$	$J_{1,8}$
11b	–	–	–	–
11c	–	4.9	3.8	3.8
11d	–	–	–	–
11e	0.5 – 0.7	4.9	3.8	3.8

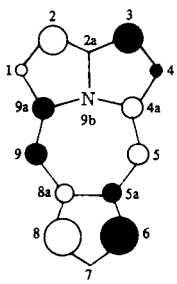
[a] TMS as internal standard; chemical shifts are given in δ (ppm). The coupling constants are given in Hz; Solvent $CDCl_3$. – [b] 2,3,4,6,7,8-H δ = 7.3 – 7.95 (together with Ph resonances).

UV Spectra[a]

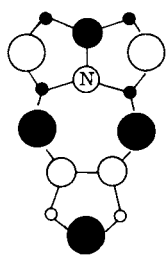
11b	257 (4.27), 304 (4.30), 312 (4.31), 349 (4.54), 395 (3.63), 420 (3.68), 446 (3.49), 512 (2.31), 534 (2.32), 550 (2.28), 578 (2.23), 642 (1.80)
11c	275 (4.38), 295 (4.39), 301 (4.40), 337 (4.51), 349 (4.65), 386 (3.87), 424 (3.72), 432 (3.65), 452 (3.58), 578 (2.34), 625 (2.35), 687 (2.05)
11d	245 (4.34), 264 (4.28), 282 (4.47), 302 (4.45), 340 (4.58), 354 (4.74), 388 (3.92), 425 (3.83), 453 (3.68), 580 (2.81), 625 (2.82), 688 (2.48)
11e	273 (4.18), 307 (4.56), 331 (4.63), 345 (4.82), 402 (3.80), 425 (3.85), 455 (3.90), 526 (2.55), 544 (2.58), 564 (2.53), 586 (2.48), 643 (2.15)

[a] Measured in ethanol; λ_{max} [nm]; lg_{10} ε in parentheses.

Scheme 3



HOMO



LUMO

MO Diagram of the Frontier Orbitals of Cyclopenta[*h*][2.2.4]cyclazine (**11a**)

Eigenvectors of the Frontier Orbitals (ε_6 and ε_7) of Cyclopenta[*h*][2.2.4]cyclazine (**11a**) (Relative Signs Indicated by Filled and Open Cycles on the Diagram)

HOMO $\varepsilon_6 = +0.38\ \beta$				LUMO $\varepsilon_7 = -0.42\ \beta$			
1,4	0.1212	5a,8a	0.1834	1,4	0.3001	5a,8a	0.2782
2,3	0.3160	6,8	0.4783	2,3	0.0377	6,8	0.0635
2a	0.0000	7	0.0000	2a	0.2843	7	0.3046
4a,9a	0.2245	9b	0.0000	4a,9a	0.0874	9b	0.2155
5,9	0.2245			5,9	0.4576		

azulene[19]). The hypsochromic effect may be attributed to preferential stabilization of the HOMO, which has relatively high one-π-electron densities at the 6- and 8-positions, and the bathochromic effect to a corresponding stabilization of the LUMO in which the one-π-electron density is relatively high at the 1- and 4-positions (Scheme 3)[20].

The role of the 2-ethoxycarbonyl group in **11e** is less clear since it has little effect on the majority of peaks in the long-wavelength band but causes a small hypsochromic shift (12 nm) in the longest wavelength (weakest) peak[21]. In view of the fact that the one-π-electron densities at the 2- and 3-positions are higher in the HOMO than in the LUMO, the shift is in the expected direction and it corresponds to the effect of a methoxycarbonyl group in the 5-position of azulene[19].

The reaction of 3*H*-pyrrolizines with vinamidinium salts provides a versatile access to [2.2.3]cyclazines which nicely complements the synthesis of [2.2.3]cyclazines from indolizines and acetylene derivatives.

We thank the *Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen* and the *University of Edinburgh* (for a Research Studentship to D.S.) and Dr. *I. H. Sadler* for help with ^{1}H NMR spectra.

Experimental Part

Melting points: Kofler apparatus, uncorrected. – ^{1}H NMR spectra: Bruker WM 300 and WH 360, tetramethylsilane as internal standard. – DMF was dried over Linde molecular sieve (type 4a). – Light petroleum refers to the fractions of b.p. 40 – 60 °C.

Diphenyl(1-phenylvinyl)phosphane Oxide (**2b**)[22]: 3.66 g (0.02 mol) of α-bromostyrene was added to 0.58 g (0.024 mol) of magnesium turnings in 60 ml of dry THF in the course of 5 h and the mixture was heated for an additional 1.5 h. 4.73 g (0.02 mol) of chlorodiphenylphosphane oxide[23] dissolved in 5 ml of dry toluene was added over a period of 0.5 h at room temperature. The reaction was completed after 10 h of refluxing. It was cooled subsequently, hydrolysed with water and extracted with toluene. Yield 2.7 g (0.012 mol, 60%). M.p. 114.5 °C (from toluene/light petroleum, 1:1) (Lit.[22] 114 – 115 °C).

2-Phenyl-3H-pyrrolizine (**3b**)[7]: 150 ml of dry toluene and 200.5 mg (5.0 mmol) of potassium hydride were stirred under nitrogen and 475.5 mg (5.0 mmol) of 2-pyrrolecarbaldehyde (**1**)[24] was added subsequently. After 30 min 1.52 g (5.0 mmol) of diphenyl(1-phenylvinyl)phosphane oxide (**2b**)[22] and a catalytic amount of dibenzo-18-crown-6[25], dissolved in 75 ml of dry toluene, was added over a period of 15 min. The mixture was stirred under reflux for 5 h, cooled and carefully hydrolysed with 50 ml of water. The toluene phase was washed three times with water, dried and evaporated. Chromatographic purification was carried out using silica gel and toluene/ethyl acetate (10:1). Yield 724.9 mg (4.0 mmol, 81%). M.p. 179 °C (from dichloromethane/*n*-pentane (1:1)) (Lit.[7] 179 °C).

The aqueous layer, upon addition of dilute hydrochloric acid, yielded 873 mg (4.0 mmol, 80%) of diphenylphosphinic acid as a colourless solid, which could be used to prepare **2b**. Yield 873 mg (4.0 mmol, 80%). M.p. 191 °C (Lit.[26] 194 – 195 °C).

Using 1.2 g (5.0 mmol) of diethyl (1-phenylvinyl)phosphonate (**2c**)[27] the yield was 407.3 mg (2.25 mmol, 45%).

Pyrrolo[2,1,5-cd]indolizine ([2.2.3]Cyclazine) (**5a**)[1b]: A solution of 300 mg (2.85 mmol) of 3*H*-pyrrolizine (**3a**)[4] in dry DMF (25 ml) was stirred under nitrogen and 710 mg (3.13 mmol) of vinamidinium salt **4a**[28] was added. After 10 min, 137 mg (2.98 mmol, 50% oil dispersion) of

sodium hydride was added in one portion. The solution was then stirred at room temperature for a further 5 min, heated slowly, and kept under reflux for 45 h. After being cooled, the solution was diluted with water (200 ml) and extracted with pentane (4 × 150 ml). The pentane extract was dried and evaporated (with minimum heating) and the residue was chromatographed on alumina. Elution with ether and vacuum sublimation (2×) of the recovered material yielded **5a**. Yield 185 mg (1.31 mmol, 46%). M.p. 60–61 °C (yellow plates) (Lit.[1b] 63.5–64.5 °C). – ^{1}H NMR spectra as reported[29].

1-Phenylpyrrolo[2,1,5-cd]indolizine (1-Phenyl[2.2.3]cyclazine) (**5b**): A solution of 181 mg (1.0 mmol) of 2-phenyl-3*H*-pyrrolizine (**3b**) in 40 ml of dry dimethylformamide (DMF) was stirred under nitrogen and 422 mg (1.2 mmol) of vinamidinium salt **4b**[28] was added in one portion. After 10 min, 72 mg (1.5 mmol, 50% oil disperion) of sodium hydride was added in small portions and the solution was heated at 60 °C for 8 h and under reflux for 20 h. Water was then added and the solution was extracted with ether. The ether extract was dried and evaporated. The residue was chromatographed on silicagel in toluene/light petroleum (3:8). Yield 90 mg (0.41 mmol, 46%). M.p. 61 °C (from cyclohexane), R_F = 0.72. – IR (KBr): 1590 (m) (aromat.), 1520 (m) cm^{-1} (aromat.). – MS (70 eV): *m/e* = 218 (25.6%, M + 1), 217 (100, M$^+$), 215 (23, M – 1).

$C_{16}H_{11}N$ (217.3) Calcd. C 88.45 H 5.10 N 6.45 Found C 88.34 H 5.29 N 6.36

1-(Phenylsulfonyl)pyrrolo[2,1,5-cd]indolizine (1-(Phenylsulfonyl)[2.2.3]cyclazine) (**5c**): 245 mg (1.0 mmol) of 2-(phenylsulfonyl)-3*H*-pyrrolizine (**3c**)[7] was treated with 422 mg (1.2 mmol) of the vinamidinium salt **4b**[28] using the conditions (with heating at 60 °C for 1 h and refluxing for 75 h) described for the preparation of the cyclazine **5b**. Chromatography on silica gel in toluene/ethyl acetate/light petroleum (8:1:1) yielded **5c**. Yield 180 mg (0.63 mmol, 63%). M.p. 189–190 °C (from dichloromethane/cyclohexane (1:1)). R_F = 0.373. – IR (KBr): 1305, 1150 cm^{-1} (SO_2). – MS (70 eV): *m/e* = 281 (100%, M$^+$), 217 (27, M – SO_2), 156 (45.6, M – SOPh), 140 (26.3, M – SO_2Ph).

$C_{16}H_{11}NO_2S$ (281.3) Calcd. C 68.31 H 3.94 N 4.98 Found C 67.93 H 3.94 N 4.87

Methyl Pyrrolo[2,1,5-cd]indolizine-1-carboxylate (Methyl [2.2.3]Cyclazine-1-carboxylate) (**5d**)[30]

Method A: A solution of 500 mg (3.1 mmol) of methyl 3*H*-pyrrolizine-6-carboxylate (**3e**)[11,31] in 25 ml of dry DMF was stirred under nitrogen and 750 mg (3.3 mmol) of the vinamidinium salt **4a**[28] was added in one portion. After 10 min, 150 mg (3.2 mmol, 50% oil dispersion) of sodium hydride was added in small portions and the solution was heated at 60 °C for 1 h and under reflux for 35 h. Water was added and the solution extracted with ether. The ether extract was dried and evaporated. The residue was chromatographed on alumina. Elution with ether/light petroleum (3:7) gave **5d**. Yield 300 mg (1.51 mmol, 49%). M.p. 60 °C (from pentane, pale yellow prisms) (Lit.[30] 59–60 °C).

Method B: 500 mg (3.1 mmol) of methyl 3*H*-pyrrolizine-6-carboxylate (**3e**)[11,31] was heated with a slight excess of 1,1,3,3-tetramethoxypropane (540 mg, 3.3 mmol) in 4 ml of acetic anhydride for 6 h. Water was added and the solution was extracted with dichloromethane. Evaporation of the extract and crystallisation of the residue from pentane yielded **5d**. Yield 160 mg (0.8 mmol, 26%). M.p. 60 °C (from pentane, pale yellow prisms) (Lit.[30] 59–60 °C).

Ethyl Pyrrolo[2,1,5-cd]indolizine-2-carboxylate (Ethyl [2.2.3]Cyclazine-2-carboxylate) (**5e**): 310 mg (1.75 mmol) of ethyl 3*H*-pyrrolizine-7-carboxylate (**3f**)[32] was treated with 400 mg (1.76 mmol) of the vinamidinium salt **4a**[28] under the conditions (with reflux for 42 h) described above for the preparation of the cyclazine **5d**. Chromatography of the crude product on alumina,

eluting with ether, yielded **5e**. Yield 180 mg (0.84 mmol, 48%). M.p. close to room temperature (yellow solid).

$C_{13}H_{11}NO_2$ Required 213.0790 Found 213.0790 (MS)

Further elution with ether yielded a mixture of two isomeric compounds,

Ethyl (Z,E)- and (E,E)-3-[3-(Dimethylamino)-2-propenylidene]-3H-pyrrolizine-7-carboxylates (**6a** and **6b**): Yield 98 mg (37.9 mmol, 22%). M.p. 151 – 152 °C (red-brown plates, from ethanol). – ^{1}H NMR: Table 3.

$C_{15}H_{18}N_2O_2$ (258.3) Calcd. C 69.7 H 7.0 N 10.8 Found C 69.6 H 6.9 N 10.6

A similar mixture of **6a** and **6b** (ca. 3.5:1) was obtained as the sole characterisable product (60%) when the same reactants as above were stirred together in DMF at room temperature for 16 h.

Hydrolysis of **5e** with KOH in aqueous methanol gave *pyrrolo[2,1,5-cd]indolizine-2-carboxylic acid* (**5f**) as yellow needles, m.p. 231 – 233 °C (Lit.[1d] 231 – 233 °C).

$C_{11}H_7NO_2$ (185.2) Calcd. C 71.35 H 3.8 N 7.6 Found C 71.2 H 4.0 N 7.3

1-Phenylcyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine (1-Phenylcyclopenta[h][2.2.4]cyclazine) (**11b**): A solution of 280 mg (1.55 mmol) of 2-phenyl-3*H*-pyrrolizine (**3b**) in 20 ml of dry DMF was stirred under nitrogen and 430 mg (1.55 mmol) of the fulvene iminium salt **10**[33] was added. After 5 min, 74 mg (1.55 mmol, 50%, oil dispersion) of sodium hydride was added and the solution was stirred at room temperature for a further 75 min and then heated slowly to the boiling point. After 18 h under reflux, the solution was evaporated and the residue was treated with water, extracted into ether and chromatographed on silica gel, in ether/light petroleum (1:4), to give **11b**. Yield 75 mg (0.28 mmol, 18%). M.p. 93 °C (yellow-brown needles, from pentane).

$C_{20}H_{13}N$ (267.3) Calcd. C 89.9 H 4.9 N 5.2 Found C 89.8 H 5.2 N 5.4

1-(Phenylsulfonyl)cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine (1-(Phenylsulfonyl)cyclopenta-[h][2.2.4]cyclazine) (**11c**): 200 mg (0.82 mmol) of 2-(phenylsulfonyl)-3*H*-pyrrolizine (**3c**)[7] and 240 mg (0.87 mmol) of the fulvene iminium salt **10**[33], in DMF, were treated with sodium hydride under the conditions (room temperature for 45 min and at reflux for 17 h) described for the preparation of the 1-phenyl compound **11b**. The product was purified by PLC on silica gel, in ether. Yield 79 mg (23.8 mmol, 30%). M.p. 248 – 250 °C (dark green needles, from butyl acetate).

$C_{20}H_{13}NO_2S$ (331.4) Calcd. C 72.5 H 3.95 N 4.2 Found C 72.3 H 3.80 N 4.4

Methyl Cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine-1-carboxylate (Methyl Cyclopenta[h]-[2.2.4]cyclazine-1-carboxylate) (**11d**): 800 mg (4.9 mmol) of methyl 3*H*-pyrrolizine-6-carboxylate (**3e**)[11,31] was treated with 2.21 g (7.9 mmol) of the fulvene iminium salt **10**[33] under the conditions (with heating at 70 °C for 30 min and at reflux for 20 h) described for the preparation of the 1-phenyl compound **11b**. The product was purified by column chromatography on silica gel, in ether/light petroleum (1:4), followed by vacuum sublimation to give **11d**. Yield 350 mg (1.4 mmol, 28%). M.p. 135 – 136 °C (green plates, from light petroleum).

$C_{16}H_{11}NO_2$ (249.3) Calcd. C 77.0 H 4.45 N 5.6 Found C 76.8 H 4.40 N 5.5

Ethyl Cyclopenta[4,5]azepino[7,1,2-cd]pyrrolizine-2-carboxylate (Ethyl Cyclopenta[h][2.2.4]-cyclazine-2-carboxylate) (**11e**): 530 mg (3.0 mmol) of ethyl 3*H*-pyrrolizine-7-carboxylate (**3f**)[32] was treated with 910 mg (3.29 mmol) of the fulvene iminium salt **10**[33] under the conditions (room temperature for 15 min and at reflux for 24 h) described for the preparation of the 1-phenyl compound **11b**. The product was purified by column chromatography on alumina, in ether, to give **11e**. Yield 395 mg (1.5 mmol, 50%). M.p. 124 – 125 °C (brown micro prisms, from ethanol).

$C_{17}H_{13}NO_2$ (263.3) Calcd. C 77.55 H 5.00 N 5.3 Found C 77.30 H 5.05 N 5.1

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