Heterocyclic Compounds with Bridgehead Nitrogen Atoms. Part 11.[1] Formation of Azocino[2,1,8-*cd*]pyrrolizines in the Reactions of Indolizines with Dimethyl Acetylenedicarboxylate

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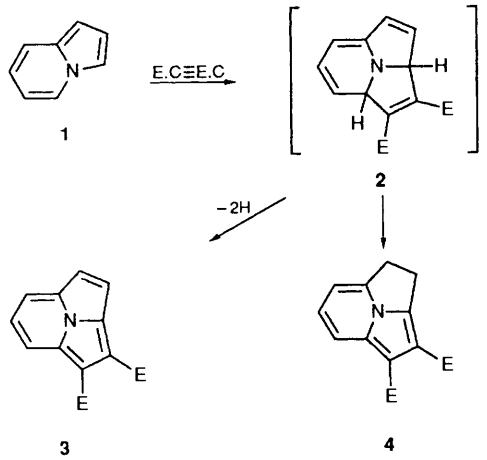
5-Methyl-1-phenylindolizine and its 1-acetyl derivative reacted with dimethyl acetylenedicarboxylate to give both 1:1- and 1:2-adducts. UV and ^{1}H NMR spectroscopy showed that these types of adducts are dihydro derivatives of pyrrolo[2,1,5-*cd*]indolizines and of azocino[2,1,8-*cd*]pyrrolizines, respectively. Contrary to previous claims, the 1:2-adducts similarly obtained from 6- and 7-methyl-2-phenylindolizines are also derivatives of the latter ring system; X-ray crystallography (of one such adduct) revealed stereochemical differences relative to the 1:2-adduct from 5-methyl-2-phenylindolizine, thus accounting for substantial associated differences in spectroscopic properties. Dehydrogenation products, previously claimed to be [2.3.4]cyclazines, are fully unsaturated azocino[2,1,8-*cd*]pyrrolizines. X-Ray crystallography showed that this hitherto unrecognised *N*-bridged [12]annulene ring system is markedly non-planar.

The reactivity of indolizines as 8π-addends in cycloadditions first came to light in the observations of Boekelheide and his co-workers[2] who made use of such a reaction in the synthesis of [2.2.3]cyclazines. In the presence of a palladium–charcoal catalyst, indolizine **1** reacted with dimethyl acetylenedicarboxylate (DMAD) to give the cyclazine diester **3** together with a smaller amount of its 3,4-dihydro derivative **4** which had presumably been formed from the initial adduct **2** by migration of both hydrogen atoms from the ring-junction positions (Scheme 1). In the absence of palladium–charcoal, compound **4** was the sole product.



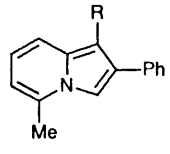
Scheme 1 E = CO_2Me

Some years ago we chose to investigate the effect of placing a methyl group in the 5-position of the indolizine, thus preventing both the aromatisation of the initial adduct and one of the hydrogen migration processes involved in the isomerisation. We now give an account of this work[3] together with the results of more recent studies (involving 3,5-unsubstituted indolizines) undertaken in response to a poorly substantiated claim[4] (concerning the structures of certain adducts) that appeared to be incompatible with our earlier conclusions.

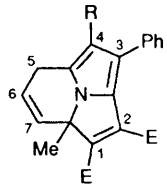
Unexpectedly, the reaction of 5-methyl-2-phenylindolizine **5a** with DMAD (1 mol equiv.) in benzene at room temperature gave not only a 1:1-adduct (5M1:1) (54%) but also a 1:2-adduct (5M1:2) (20%). Although the former could not be converted into the latter by further reaction with DMAD, the yields of the two adducts were reversed in relative magnitude (20% and 43% respectively) when the indolizine **5** was treated with 2 mol equiv. DMAD.

The structure **6a** assigned to 5M1:1 was based on its ^{1}H NMR spectrum (Table 1) which showed, *inter alia*, the presence of a methyl group joined to non-aromatic carbon (δ 1.66), a singlet (δ 6.32) attributable to the pyrrole proton at C-4, and a four-spin system of the type ($CH{=}CHCH_2$) which was necessarily derived from the unsubstituted part of the indolizine 6-membered ring. Deshielding of the methylene protons (av. δ 3.4) indicated the position of the CH_2 group at C-5, next to the aromatic pyrrole ring, rather than at C-7. Other workers[4] have since reported indolizine–DMAD adducts of analogous structure.

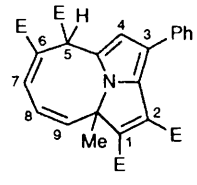
Given an established structure **6a** for the 1:1-adduct, it was



5 **a**; R = H
b; R = COMe



6 **a**; R = H
b; R = COMe



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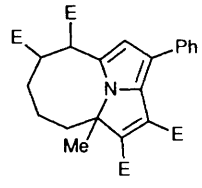

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possible to elucidate the structure **7** of the 1:2-adduct (5M1:2) on the basis of the following comparative evidence. (i) The presence of a 1,2-di(methoxycarbonyl)-3*H*-pyrrolizine substructure was apparent from the UV spectrum of 5M1:2 in which two of the absorption bands were similar, in form and wavelength, to those of 5M1:1. In addition, however, there was evidence for a second chromophore, absent in 5M1:1 and

Table 1 ^{1}H NMR spectroscopic data[a,b] of pyrrolo[2,1,5-*cd*]indolizines and azocino[2,1,8-*cd*]pyrrolizines

Compd.	δ_4	δ_5	δ_6	δ_7	δ_8	δ_9	δ_{7a} or δ_{9a}	|J|/Hz[c]
6a	6.32(s)	3.35(br d) 3.45(dd)	6.06(ddd)	6.68(dd)			(1.66)s	$J_{5,5'}$ 20.0, $J_{6,7}$ 9.4, $J_{5,6}$ 5.4 $J_{5'6}$ 2.1, $J_{5',7}$ 2.7
6b	(2.00)s	3.41(ddd) 4.21(dd)	6.11(ddd)	6.66(dd)			(1.65)s	$J_{5,5'}$ 21.3, $J_{6,7}$ 9.4 $J_{5,6}$ 5.6, $J_{5'6}$ 1.8
				NOE			*	$J_{5',7}$ 3.3
7	6.75(s)	4.91(s)		6.90(d)	6.05(dd)	6.76(d)	(1.72)s	$J_{7,8}$ 6.2, $J_{8,9}$ 13.4
17a	7.25(d)	4.64(dd)		7.71(m)	6.37(m)	(1.73)t	5.06(d)	$J_{7,8}$ 2.2, $J_{5,9a}$ ~2.0, $J_{4,5}$ ~1.2
	(s)	*					(s)	$J_{7,CH_3} \simeq J_{8,CH_3}$ ~1.8
17b	7.19(d)	4.66(dd)		7.61(m)	(1.99)dt	5.54(dm)	5.03(ddm)	$J_{9,9a}$ 6.95, $J_{5,9a}$ ~2.0
	*	(d)						$J_{4,5}$ ~1.1 $J_{7,9}$ ~0.9
	(s)	*					(br d)	J_{7,CH_3} ~0.9 J_{9,CH_3} ~1.6
				*	dd	(dq)	(ddq)	$J_{7,9a}$ ~0.8 J_{9a,CH_3} ~0.8
				(t)	*	(dd)	(ddd)	
				(br)	br	*	(br m)	
				(br)	dd	(m)	*	
10	(1.88)s			2.57(ddd)	5.86(ddd)	6.36(dd)	(1.67)s	$J_{7,7'}$ 13.9, $J_{8,9}$ 11.4
		(br)		3.09(dd)				$J_{7,8}$ 10.1, $J_{7',8}$ 5.1
						NOE	*	$J_{7',9}$ 2.8
18a	7.40(s)			7.28(m)	6.35(m)	(1.96)t		$J_{7,8}$ 3.6, J_{8,CH_3} ~1.5
								J_{7,CH_3} ~1.9
18b	7.27(s)			7.17(m)	(2.06)dd	6.22(m)		$J_{7,9} \simeq J_{7,CH_3}$ ~0.9
								J_{9,CH_3} ~1.6

[a] In $CDCl_3$; δ values in parentheses refer to protons in substituent groups. [b] All compounds showed absorptions due to Ph and OMe protons but these are omitted from the table. [c] Coupling constants are based on first order analyses of the spectra and may be subject to small inaccuracies, particularly for spectra rich in long-range coupling. * Asterisks indicate positions of irradiation in decoupling or NOEDS experiments; the effects of the former are indicated as changed multiplicities of the affected signals.

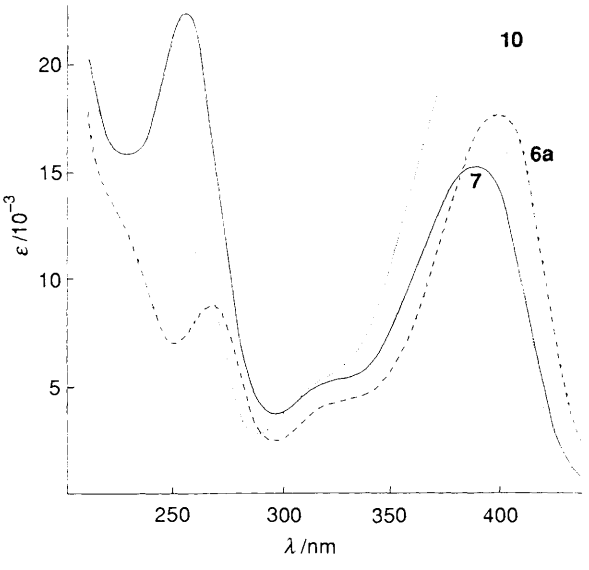
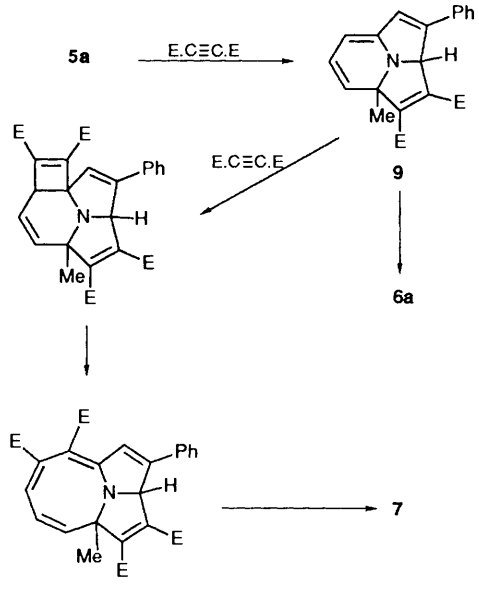


Fig. 1 UV spectra of the adducts **6a** and **7** and of the tetrahydro adduct **10** in ethanol



Scheme 2 E = CO_2Me

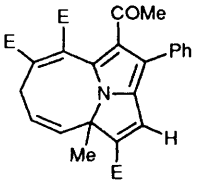
absorbing strongly at λ 256 nm (Fig. 1). (ii) Catalytic hydrogenation of 5M1:2 gave a tetrahydro derivative **8** in which the additional chromophore was absent, the UV spectrum (Fig. 1) being even more closely similar to that of 5M1:1. This was consistent with the removal of a conjugated diene moiety forming part of a 2,4-dienoic ester chromophore (*cf.* methyl hexa-2,4-dienoate, λ_{max}(nm 258). (iii) The ^{1}H NMR spectrum of 5M1:2 showed C–CH_3 (δ 1.71) and pyrrole proton (δ 6.75) singlets similar to those of 5M1:1 but the four-spin system ($CH{=}CHCH_2$) of the latter was replaced by a three-spin system of the type ($CH{=}CHCH{=}$) together with a singlet at δ 4.91, attributable to the isolated CH–CO_2Me of structure **7**. The presence of three vicinal olefinic protons, the most shielded of which was in the central position, provided further evidence for the dienoic ester grouping. It is noteworthy that both of the vicinal coupling constants (6.2 and 13.4 Hz) were substantial in magnitude.

The formation of the adducts **6a** and **7** can be readily explained on the basis of Scheme 2. The initial [8 + 2]cyclo addition leads to an entirely non-aromatic 2,7a-dihydro-[2.2.3]cyclazine **9** which may isomerise by H-transfer to the more stable 5,7a-dihydro compound **6a** containing one aromatic (pyrrole) ring, or may undergo ring expansion, as for 1,2-dihydropyridines of less complex structure,[5] before the transfer of hydrogen.

1-Acetyl-5-methyl-2-phenylindolizine **5b** reacted similarly with DMAD in boiling benzene, yielding a 1:1- and a 1:2-adduct. The 1:1-adduct **6b** was analogous to 5M1:1 **6a**, as shown by its ^{1}H NMR spectrum (Table 1), but the 1:2-adduct **10**, while based on the same tricyclic skeleton as 5M1:2, was a 7,9a- rather than a 5,9a-dihydro derivative. The ^{1}H NMR spectroscopic data of **10** (Table 1), including the NOE at δ 6.36 caused by irradiation of the 9a-methyl group, showed the presence of a four-spin system ($CH{=}CHCH_2$)

different from that of **6b** and having its terminal CH-group (rather than CH_2) at C-9.

Shortly after the completion of the foregoing work a report[6] appeared of the related reaction of 3-methyl-2-phenylindolizine **11** leading to two stereoisomeric 1:2-adducts, **12** and **13**, which were conclusively identified by X-ray crystallography of the minor isomer **13**. This corroborated our findings with respect to



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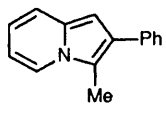

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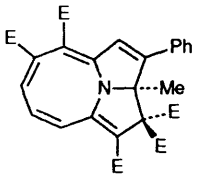

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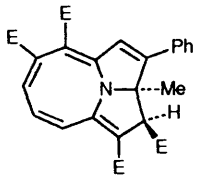

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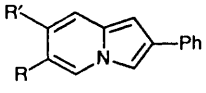
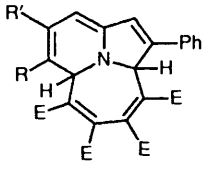


14 **a**; R = Me, R′ = H
b; R = H, R′ = Me



15 **a**; R = Me, R′ = H
b; R = H, R′ = Me

the reaction of 5-methyl-2-phenylindolizine and we decided not to pursue our investigations further at that time. More recently, however, Yamashita and his co-workers[4] claimed that the reactions of DMAD with 6- or 7-methyl-2-phenylindolizine **14a**, **b** afford, *inter alia*, 1:2-adducts **15a**, **b** of a quite different structural type. Unfortunately, these structures were completely unsupported by spectroscopic evidence. Dehydrogenation of the adducts [with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)] was said to yield fully unsaturated [2.3.4]cyclazines **6a**, **b** but the properties of these red dehydrogenation products did not match those of known[7] [2.3.4]cyclazines (green or blue). Accordingly, we undertook to reinvestigate the structures of the 1:2-adducts (6M1:2 and 7M1:2) derived from 6- and 7-methyl-2-phenylindolizines **14a**, **b** by reaction with DMAD.

In the work of Yamashita *et al.*,[4] these adducts were best prepared (50 and 38%, respectively) by reaction of the indolizines **14a** and **14b** with an excess of DMAD in acetone at room temperature. However, after failing to isolate more than traces of the adducts under these conditions, we obtained them in acceptable amounts (35 and 11%, respectively) from reactions in anhydrous ether at room temperature for 24 h followed by a period under reflux. The 1:2-adducts crystallised directly from the cooled solutions and the need for tedious chromatographic separation was thus avoided. The adducts obtained in this way differed appreciably in their melting points from those reported by Yamashita *et al.* but they were convertible, as stated,[4] into red dehydrogenated products that showed melting points in reasonable agreement with the reported values. It seems, therefore, that the adducts obtained in our work, though perhaps not identical with those of the Japanese workers, could not have differed from them other than stereochemically.

Unfortunately, the spectroscopic features of 6M1:2 and 7M1:2 were not structurally definitive since they differed in

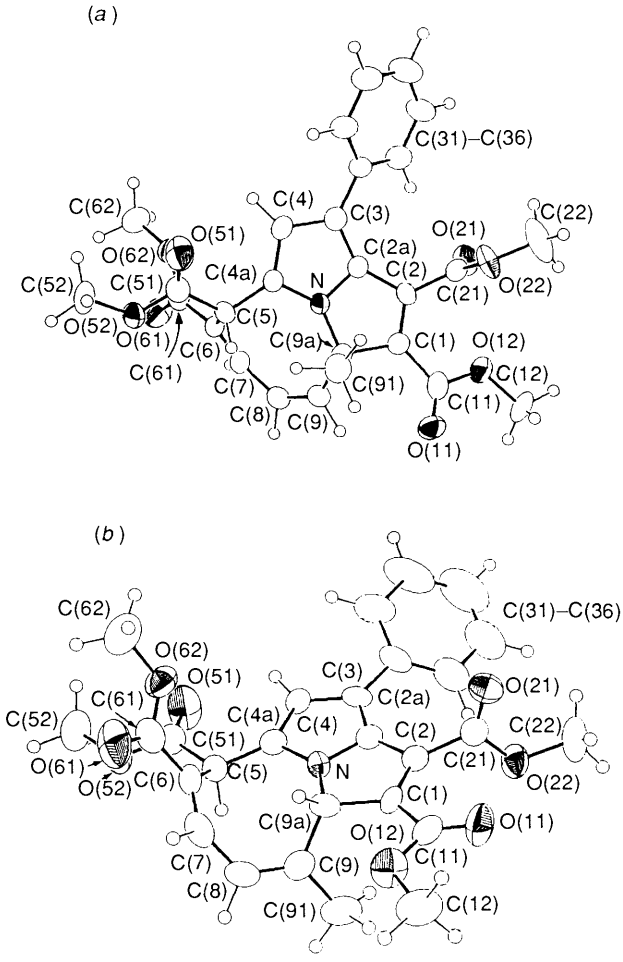


Fig. 2 Molecular structures of the 5,9a-dihydroazocino[2,1,8-*cd*]pyrrolizines **7** (*a*) and **17a** (*b*) showing crystallographic numbering schemes

several respects from those of 5M1:2 **7**. The UV spectra were similar to that of **7** in showing absorption characteristic of a 1,2-di(methoxycarbonyl)-3*H*-pyrrolizine substructure but they lacked the band at λ/nm 256 expected for a dienoic ester chromophore. The ^{1}H NMR spectra of 6M1:2 and 7M1:2 (Table 1) showed five signals due to protons derived from the original indolizine nuclei but these did not correlate well with the corresponding proton signals of 5M1:2: firstly, the chemical shift differences were substantial; secondly, none of the signals in the spectrum of 6M1:2 showed splitting greater than 2.2 Hz (though $^3J_{7,8}$ was 6.2 Hz in 5M1:2); and thirdly, long range couplings, absent in the spectrum of 5M1:2, were abundant in those of 6M1:2 and 7M1:2. This last feature was only partly due to inclusion of the CCH_3 protons in the spin system.

A better correlation was apparent in the ^{13}C NMR spectra of these three 1:2-adducts (Table 2). The signals due to C-4, 5 and 9a of 5M1:2 were readily identifiable at δ 115.1, 42.6 and 68.3, respectively, and since close counterparts were present in the spectra of 6M1:2 (δ 112.7, 42.7 and 62.5) and 7M1:2 (δ 113.0, 42.8 and 60.5) it seemed probable that all three compounds had gross structures (**7**, **17a** and **17b**) of the same type.

A proof of this tentative conclusion and an explanation of the spectroscopic differences referred to above were finally provided by X-ray structure analysis of 6M1:2 and 5M1:2. The results (Fig. 2 and Tables 3 and 4) show that both molecules are indeed derivatives of 5,9a-dihydroazocino[2,1,8-*cd*]pyrrolizine but that they differ stereochemically as well as in the position of the methyl substituent. The 5-methoxy carbonyl group is

Table 2 ^{13}C NMR spectroscopic data[a,b] of 5,9a-dihydroazocino[2,1,8-*cd*]pyrrolizines

	Compound 7					Compound **17a**						
			[M][f]					[M][f]					
Carbon position	δc^d	M[e]	δ_H 4.8 5-H	6.7 6.8 4,9-H	6.9 7-H	$\delta_c{}^d$	M[e]	δ_H 1.73 CH_3	4.64 5-H	7.71 7-H	6.37 8-H	5.05 9a-H	Compound **17b**[c] $\delta_c{}^d$
1	(133.7)	s				126.0	d					s	(125.8)
2	(135.5)	s				139.1	d					s	137.9
2a	127.8	d		s		130.3	d						130.2
3	123.9	m		t		123.7	br					+	(123.5)
4	115.1	Dd	D			112.7	D		D*				113.0
4a	129.9	t	d	d		125.4	m		+			+	(125.2)
5	42.6	Dd			D	42.7	Dd			D			42.8
6	132.0	t[g]	d[g]			124.9	m		brd	+	d		(?)
7	132.7	Ddd[g]	Dd[g]	Dd[g]		140.6	brD		D*		Dd		141.8
8	122.1	D				126.9	Dm[g]	Dd[g]					139.8
9	138.3	brD			D*	131.5	m	t			+	+	118.6
9a	68.3	m				62.5	Dm	Dd			Dd		60.5
o-Ph	127.4	Dt				127.5	Dt						127.7
m-Ph	128.0	Dd				128.2	Dd						128.2
p-Ph	126.4	Dt				126.5	Dt						126.5
i-Ph	134.0	t				134.5	t						134.7
CO	161.7	m				162.3	m						162.2
CO	164.6	m				164.7	m						164.8
CO	164.8	m				165.2	m						165.3
5-CO	168.7	m	+			168.9	m		+				168.8
C-CH_3	28.6	Q				18.8	Qm				Qd	Qd	20.3

[a] In $CDCl_3$. [b] All compounds showed absorptions due to four OCH_3 carbons but these are omitted from the table. [c] Assignments aided by DEPT spectra and by analogy with **17a**; one quaternary resonance not observed (probably C-1, 3, 4a, or 6). [d] Parentheses indicate uncertain assignments. [e] M = Multiplicity in fully proton-coupled spectrum; upper case letters refer to one-bond C–H coupling and lower case letters to longer range coupling; br = broad. [f] [M] = Changed multiplicity caused by selective, low power proton irradiation at the frequencies (δ_H) indicated; + indicates small effect, not easily definable; * indicates narrowing of lines; [g] resonance partially obscured owing to overlap.

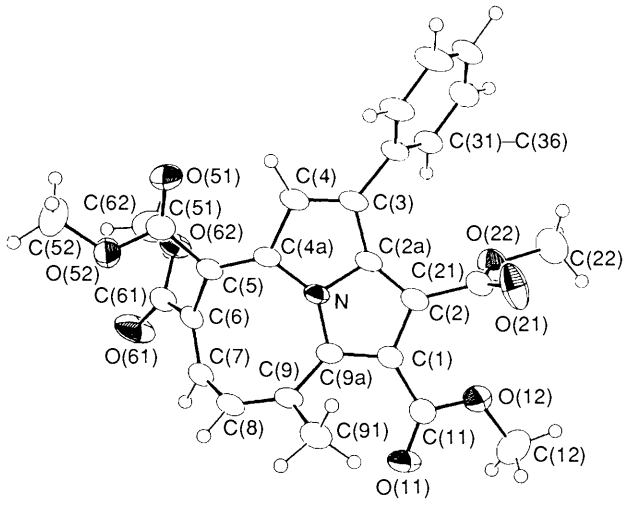


Fig. 3 Molecular structure of the azocino[2,1,8-*cd*]pyrrolizine **18a** showing crystallographic numbering scheme

trans to the 9a-methyl in 5M1:2 and *cis*- to the 9a-hydrogen in 6M1:2. In parallel with this configurational difference, there is also a conformational difference, mainly confined to the azocine rings of the two isomers and such that the torsion angle C(6)–C(7)–C(8)–C(9) is 37.6° in 5M1:2 and 60.6° in 6M1:2. There can be little doubt that the much larger torsion angle in the latter adduct is responsible for the absence of diene conjugation and for the low value of the vicinal proton coupling constant $^3J_{7,8}$. At the same time, the opportunities for four- and five-bond coupling are likely to be increased with increased puckering of the azocine ring. Related examples of this effect are seen in the spectra of cyclooctatetraenes[8] and nonafulvenes.[9]

In the light of the established structure **17a**, both the ^1H and ^{13}C NMR spectra of 6M1:2 were assigned, with few remaining ambiguities, by means of $^{13}C\{^1H\}$ double resonance experiments (Table 2) with selective low power proton irradiation, such that only the long range CH coupling was affected.

Dehydrogenation of **17a** and **17b** with DDQ in boiling benzene yielded the fully unsaturated azocino[2,1,8-*cd*]pyrrolizines **18a** and **18b** as deep red, air-stable, crystalline solids. These compounds are *N*-bridged [12]annulenes[7,10] which, if their structures were not too far distorted from planarity, might be expected to show evidence of antiaromaticity. However, the NMR spectroscopic absorptions (Table 1) of the three remaining protons joined to the annulene nucleus showed no evidence of ring current effects, being only minimally increased or decreased in frequency relative to their counterparts in the precursor dihydro compounds. The X-ray structure (Fig. 3 and Table 5) of **18a** showed that this is due to non-planarity in the azocine ring which has large torsion angles about the formally single carbon–carbon bonds; the angle C(6)–C(7)–C(8)–C(9), for example, is even larger (62.7°) than the corresponding angle in the dihydro compound **17a**. These features, and the bond lengths, are consistent with the mode of bond fixation shown in formula **18**. The red colour of these compounds is evidently due to conjugation in the 3-methyl-3*H*-pyrrolizine moiety which shows relatively small deviations from planarity.

Although these [12] annulene derivatives might appear to represent a new cyclazine ring system ([2.2.5]cyclazine) they do not fall within the definition of cyclazines originally proposed by Boekelheide[11] because of their non-planar structures.

Experimental

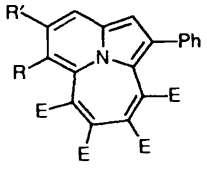
Unless otherwise stated in Table 2, ^{13}C NMR data were collected at 50.3 MHz. Alumina for chromatography was

Table 3 Atomic coordinates with esds for **7**

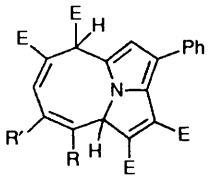
	x	*y*	*z*
N	0.105 25(25)	−0.234 98(17)	0.689 90(16)
C(1)	0.188 3(3)	−0.122 21(21)	0.575 32(19)
C(2)	0.196 4(3)	−0.057 23(21)	0.667 59(20)
C(2a)	0.153 5(3)	−0.126 84(21)	0.743 21(19)
C(3)	0.160 1(3)	−0.129 01(22)	0.849 34(21)
C(4)	0.112 7(3)	−0.243 09(22)	0.858 35(20)
C(4a)	0.082 9(3)	−0.307 62(21)	0.759 09(20)
C(5)	−0.000 1(3)	−0.426 10(20)	0.716 08(19)
C(6)	−0.193 1(3)	−0.432 52(20)	0.667 21(20)
C(7)	−0.249 9(3)	−0.406 11(21)	0.572 18(20)
C(8)	−0.154 5(3)	−0.372 85(22)	0.491 90(21)
C(9)	0.001 9(3)	−0.309 82(21)	0.495 25(21)
C(9a)	0.147 2(3)	−0.245 57(21)	0.585 14(19)
C(11)	0.230 5(3)	−0.086 45(23)	0.476 53(22)
O(11)	0.264 81(25)	−0.147 20(16)	0.407 84(15)
O(12)	0.230 58(25)	0.022 90(16)	0.478 04(15)
C(12)	0.274 4(4)	0.066 95(25)	0.386 95(22)
C(21)	0.233 7(3)	0.068 69(22)	0.687 49(20)
O(21)	0.121 78(24)	0.123 55(16)	0.683 38(16)
O(22)	0.403 80(23)	0.108 59(15)	0.709 65(17)
C(22)	0.453 2(4)	0.230 06(25)	0.725 0(3)
C(31)	0.209 26(17)	−0.035 19(11)	0.939 61(10)
C(32)	0.307 41(17)	−0.051 40(11)	1.035 62(10)
C(33)	0.357 02(17)	0.035 39(11)	1.121 44(10)
C(34)	0.308 49(17)	0.138 38(11)	1.111 24(10)
C(35)	0.210 33(17)	0.154 58(11)	1.015 21(10)
C(36)	0.160 73(17)	0.067 80(11)	0.929 40(10)
C(51)	0.036 9(3)	−0.506 05(22)	0.793 36(21)
O(51)	0.146 7(3)	−0.484 66(17)	0.873 85(17)
O(52)	−0.064 43(24)	−0.606 13(15)	0.757 65(14)
C(52)	−0.039 1(4)	−0.691 65(24)	0.823 70(24)
C(61)	−0.327 9(3)	−0.461 84(21)	0.727 62(21)
O(61)	−0.480 10(25)	−0.499 24(19)	0.689 58(17)
O(62)	−0.263 17(23)	−0.440 76(16)	0.832 26(15)
C(62)	−0.384 8(4)	−0.467 3(3)	0.899 20(23)
C(91)	0.313 9(3)	−0.296 50(22)	0.588 70(23)

Table 4 Atomic coordinates with esds for **17a**

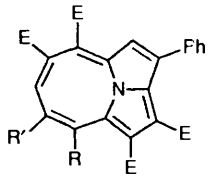
	x	*y*	*z*
N	0.314 5(8)	−0.005 6(3)	0.272 9(7)
C(1)	0.077 5(9)	0.031 7(4)	0.178 1(8)
C(2)	0.181 5(9)	0.072 3(4)	0.198 2(8)
C(2a)	0.331 8(9)	0.048 7(4)	0.260 7(8)
C(3)	0.486 9(9)	0.059 8(4)	0.302 0(8)
C(4)	0.560 2(9)	0.009 4(4)	0.339 0(8)
C(4a)	0.454 8(8)	−0.031 1(4)	0.320 7(8)
C(5)	0.466 4(9)	−0.089 8(4)	0.353 3(8)
C(6)	0.351 9(9)	−0.125 8(4)	0.246 1(8)
C(7)	0.213 8(10)	−0.137 2(4)	0.239 3(9)
C(8)	0.146 0(9)	−0.109 9(4)	0.316 9(9)
C(9)	0.118 4(9)	−0.057 9(4)	0.313 5(9)
C(9a)	0.155 7(8)	−0.022 8(4)	0.218 9(8)
C(11)	−0.087 1(9)	0.041 2(4)	0.108 7(8)
O(11)	−0.147 5(7)	0.082 8(3)	0.073 4(7)
O(12)	−0.159 3(7)	−0.007 2(3)	0.096 6(6)
C(12)	−0.325 8(9)	−0.004 2(5)	0.036 5(9)
C(21)	0.147 7(10)	0.127 0(4)	0.143 1(9)
O(21)	0.148 1(8)	0.140 3(3)	0.043 5(7)
O(22)	0.114 4(7)	0.161 0(3)	0.219 2(6)
C(22)	0.074 1(12)	0.215 7(4)	0.169 8(11)
C(32)	0.505 3(6)	0.160 09(25)	0.338 4(5)
C(33)	0.581 7(6)	0.209 08(25)	0.349 0(5)
C(34)	0.717 1(6)	0.210 34(25)	0.333 1(5)
C(35)	0.776 1(6)	0.162 61(25)	0.306 5(5)
C(36)	0.699 7(6)	0.113 62(25)	0.295 8(5)
C(31)	0.564 3(6)	0.112 36(25)	0.311 7(5)
C(51)	0.627 7(10)	−0.111 8(4)	0.403 3(9)
O(51)	0.738 6(8)	−0.084 9(3)	0.439 3(9)
O(52)	0.628 2(7)	−0.165 5(3)	0.406 3(6)
C(52)	0.776 4(10)	−0.190 3(4)	0.449 8(10)
C(61)	0.395 9(10)	−0.152 4(4)	0.150 5(9)
O(61)	0.338 4(9)	−0.191 0(3)	0.087 8(7)
O(62)	0.510 6(8)	−0.124 7(3)	0.138 0(6)
C(62)	0.567 0(13)	−0.147 9(5)	0.048 8(10)
C(91)	0.051 2(10)	−0.029 6(5)	0.395 5(9)



16 **a**; R = Me, R′ = H
b; R = H, R′ = Me



17 **a**; R = Me, R′ = H
b; R = H, R′ = Me



18 **a**; R = Me, R′ = H
b; R = H, R′ = Me

Laporte Type H or UG deactivated by treatment with 5% aqueous acetic acid (0.06 cm^3 per g alumina). Silica for TLC was Merck Kieselgel G. Light petroleum refers to the fraction of b.p. 40–60 °C and ether refers to diethyl ether.

Reaction of 5-Methyl-2-phenylindolizine **5a** *with Dimethyl Acetylenedicarboxylate.*—A solution of the indolizine **5a** (0.5 g, 2.4 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.35 g, 2.5 mmol), in benzene (100 cm^3), was kept at room temperature for 24 h, evaporated (to 10 cm^3) and chromatographed on alumina. Elution with benzene gave *dimethyl 5,7a-dihydro-7a-methyl-3-phenylpyrrolo*[2,1,5-cd]*indolizine-1,2-dicarboxylate* **6a** (0.45 g, 54%) as pale yellow crystals, m.p. 107 °C (from methanol) (Found: C, 72.1; H, 5.5; N, 4.0%; M^+, 349. $C_{21}H_{19}NO_4$ requires C, 72.1; H, 5.5; N, 4.0%; *M*, 349); δ_C 25.3 (CH_2), 27.4 (7a-CH_3), 51.5, 52.2, (2 × OCH_3), 64.8 (C-7a), 108.3 (C-4), 122.4, 126.5 (2 × CH), 127.2, 128.3, 130.0 (3 × CH, phenyl), 132.0, 134.55, 134.6, 137.1, (4 × quat. C), 162.5 and 165.4 (2 × C=O): one of the expected signals is not observed, possibly due to overlap. Further elution with benzene gave *tetramethyl 5,9a-dihydro-9a-methyl-3-phenylazocino*[2,1,8-cd]*pyrrolizine-1,2,5,6-tetracarboxylate* **7** (0.24 g, 20%) as prisms, m.p. 168–169 °C (from methanol) (Found: C, 65.9; H, 5.2; N, 2.8%; M^+, 491. $C_{27}H_{25}NO_8$ requires C, 66.0; H, 5.1; N, 2.8%; *M*, 491).

A similar reaction of the indolizine **5a** with DMAD (2 mol equiv) gave the same two adducts **6a** and **7** (20% and 43%, respectively).

Hydrogenation of the Adduct **7**.—The adduct (0.2 g), in ethanol (25 cm^3), was hydrogenated at atmospheric pressure in the presence of a palladium-on-charcoal catalyst (0.05 g). When absorption of hydrogen had ceased, the solution was filtered and evaporated. Recrystallisation of the residue from ethanol gave *tetramethyl 5,6,7,8,9,9a-hexahydro-9a-methyl-3-phenylazocino*[2,1,8-cd]*pyrrolizine-1,2,5,6-tetracarboxylate* **8** (0.15 g, 75%), m.p. 183–185 °C (Found: C, 65.4; H, 5.7; N, 2.7%; M^+, 495. $C_{27}H_{29}NO_8$ requires C, 65.4; H, 5.9; N, 2.8%; *M*, 495); δ_H(100 MHz; $CDCl_3$) 1.7 (3 H, s, 9a-CH_3), 2–4 (*ca.* 7 H, complex m, 6-, 7-, 8- and 9-H), 4.8 (1 H, d, 5-H), 6.7 (1 H, s, 4-H) and OCH_3 and Ph proton signals.

Reaction of 1-Acetyl-5-methyl-2-phenylindolizine **5b** *with Dimethyl Acetylenedicarboxylate.*—A solution of the indolizine[12] **5b** (0.193 g, 0.78 mmol) and DMAD (0.23 g, 1.6 mmol) in

Table 5 Atomic coordinates with esds for **18a**

	x	*y*	*z*
N	0.206 8(3)	0.021 9(3)	0.261 50(22)
C(1)	0.299 0(3)	−0.089 3(3)	0.128 8(3)
C(2)	0.385 6(3)	−0.130 4(3)	0.200 9(3)
C(2a)	0.323 3(3)	−0.063 6(3)	0.284 6(3)
C(3)	0.314 4(4)	−0.063 8(3)	0.400 2(3)
C(4)	0.196 0(4)	0.015 9(3)	0.443 2(3)
C(4a)	0.132 5(3)	0.086 7(3)	0.350 8(3)
C(5)	0.049 2(3)	0.207 3(3)	0.335 3(3)
C(6)	0.046 0(3)	0.304 1(3)	0.215 3(3)
C(7)	0.010 9(4)	0.280 0(4)	0.136 9(3)
C(8)	−0.032 4(4)	0.155 0(4)	0.150 1(3)
C(9)	0.044 5(4)	0.031 6(4)	0.160 7(3)
C(9a)	0.183 1(3)	−0.001 4(3)	0.172 9(3)
C(11)	0.334 2(4)	−0.125 1(3)	0.020 6(3)
O(11)	0.262 4(3)	−0.095 3(3)	−0.039 92(22)
O(12)	0.461 7(3)	−0.197 8(3)	−0.005 00(23)
C(12)	0.509 1(5)	−0.241 0(5)	−0.108 3(4)
C(21)	0.505 4(4)	−0.242 6(4)	0.200 0(3)
O(21)	0.491 6(3)	−0.361 4(3)	0.241 2(3)
O(22)	0.625 74(25)	−0.194 8(3)	0.152 82(24)
C(22)	0.746 4(4)	−0.297 0(5)	0.154 2(5)
C(31)	0.418 63(20)	−0.137 87(23)	0.459 53(18)
C(32)	0.560 29(20)	−0.127 13(23)	0.396 57(18)
C(33)	0.656 73(20)	−0.191 19(23)	0.455 16(18)
C(34)	0.611 51(20)	−0.266 00(23)	0.576 70(18)
C(35)	0.469 86(20)	−0.276 75(23)	0.639 65(18)
C(36)	0.373 42(20)	−0.212 68(23)	0.581 07(18)
C(51)	−0.026 8(4)	0.263 5(4)	0.436 7(3)
O(51)	−0.011 1(3)	0.221 7(3)	0.532 10(22)
O(52)	−0.120 2(3)	0.370 3(3)	0.407 77(22)
C(52)	−0.203 9(5)	0.436 5(5)	0.498 0(4)
C(61)	0.090 8(4)	0.439 8(3)	0.179 3(3)
O(61)	0.064 7(4)	0.541 2(3)	0.103 6(3)
O(62)	0.171 4(3)	0.437 34(23)	0.237 98(21)
C(62)	0.226 8(6)	0.563 2(4)	0.204 5(4)
C(91)	−0.014 3(4)	−0.089 2(4)	0.170 4(4)

benzene (15 cm^3) was heated under reflux for 8 h. The solution was evaporated and the residue was chromatographed on alumina. Elution with dichloromethane–light petroleum (4:1) gave a pale yellow solid (0.075 g) which was recrystallised, first from methanol (crystals tend to retain water), and then from cyclohexane–ethyl acetate to yield *dimethyl* 4-*acetyl*-5,7a-*dihydro*-7a-*methyl*-3-*phenylpyrrolo*[2,1,5-cd]*indolizine*-1,2-*dicarboxylate* **6b**, as prisms, m.p. 145–146 °C (Found: C, 70.8; H, 5.4; N, 3.5%; M^+, 391.1425. $C_{13}H_{21}NO_5$ requires C, 70.6; H, 5.4; N, 3.6%; *M*, 391.1420). Further elution with dichloromethane gave a crude solid (0.085 g) which, after recrystallisation from methanol, afforded *tetramethyl* 4-*acetyl*-7,9a-*dihydro*-9a-*methyl*-3-*phenylazocino*[2,1,8-cd]*pyrrolizine*-1,2,5,6-tetracarboxylate **10** as prisms, m.p. 189–190 °C (Found: C, 65.3; H, 5.1; N, 2.7%; M^+, 533. $C_{29}H_{27}NO_9$ requires C, 65.3; H, 5.1; N, 2.6%; *M*, 533); δ_C 24.4 (9a-CH_3), 28.5 (CH_2), 29.9 (CH_3CO), 51.9, 52.1, 52.3, 52.5 (4 × OCH_3), 73.2 (C-9a), 122.4 (quat C), 122.9 (CH, C-8 and -9), 127.0 (quat C), 128.0 (CH, phenyl), 128.6 (quat C), 130.2, 130.9 (2 × CH, phenyl), 132.2, 132.4, 132.7, 124.6, 134.8, 140.9 (6 × quat C), 161.4, 163.3, 165.2, 167.6 [4 × C=O (ester)] and 194.9 [C=O (ketone)]; λ_{max}(EtOH)/nm 213, 262, and 355, log ε 4.33, 4.22 and 4.31.

Reactions of 6- *and* 7-*Methyl*-2-*phenylindolizines* **14a** *and* **14b** *with Dimethyl Acetylenedicarboxylate.*—(*a*) The indolizine **14a** (1.84 g, 8.9 mmol) was stirred with a solution of DMAD (4.80 g, 34 mmol) in sodium-dried ether (90 cm^3) for 24 h at room temperature. A yellow–brown amorphous solid (0.24 g) which had formed was filtered off and shown by TLC to be mainly chromatographically immobile. At this stage, the ethereal filtrate showed 3 principal yellow components, of which the one of highest R_F was dominant. The solution was heated under reflux for 7 h, the yellow component of lower R_F became dominant and started to crystallise. After a further 16 h at room temperature, this product was filtered off and a second crop was obtained by concentration of the mother liquor (to *ca.* 1/3). The crude yellow solid (1.54 g, 35%) was recrystallised from acetone to yield *tetramethyl* 5,9a-*dihydro*-9-*methyl*-3-*phenylazocino*[2,1,8-cd]*pyrrolizine*-1,2,5,6-*tetracarboxylate* **17a** as pale yellow needles, m.p. 187–188 °C (lit.,[4] m.p. for putative **15a** 197–198 °C) (Found: C, 65.9; H, 5.1; N, 2.9%; M^+, 491.1580. $C_{27}H_{25}NO_8$ requires C, 66.0; H, 5.1; N, 2.85%, *M*, 491.1580); λ_{max}(EtOH)/nm 204, 250sh, 320sh and 388, log ε 4.53, 4.10, 3.68 and 4.17.

(*b*) The indolizine **14b** (1.84 g) and DMAD (4.80 g) in sodium-dried ether were treated as in (*a*) and yielded a crude orange product (0.5 g, 11%). (A second crop from the mother liquor was of very poor quality and was discarded.) Recrystallisation of the orange product from acetone yielded *tetramethyl* 5,9a-*dihydro*-8-*methyl*-3-*phenylazocino*[2,1,8-cd]*pyrrolizine*-1,2,5,6-*tetracarboxylate* **17b** as pale yellow prisms, m.p. 178–179 °C (lit.,[4] m.p. for putative **15b** 212–214 °C) (Found: C, 66.1; H, 5.2; N, 2.8%; M^+, 491.1589); λ_{max}/nm 206, 150sh, 330sh and 387, log ε 4.45, 4.15, 3.77, and 4.12.

Dehydrogenation of the Adducts **17a** *and* **17b**.—(*a*) A solution of the adduct **17a** (0.5 g) and DDQ (0.4 g) in benzene (50 cm^3) was heated briefly under reflux until it became deep red. After being allowed to cool slowly, the solution was filtered to remove a pale solid (0.21 g), evaporated to a small volume, and chromatographed on alumina. Elution with dichloromethane, evaporation of the eluate, and trituration of the residue with ether yielded *tetramethyl* 9-*methyl*-3-*phenylazocino*[2,1,8-cd]-*pyrrolizine*-1,2,5,6-*tetracarboxylate* **18a** (0.46 g, 92%) as deep red prisms (from cyclohexane–ethyl acetate), m.p. 191–192 °C (lit.,[4] m.p. for putative **16a** 186–189 °C) (Found: M^+, 489.1429. $C_{27}H_{23}NO_8$ requires *M*, 489.1424); δ_C 24.9, 51.7, 52.0, 52.2, 116.1, 117.3, 119.5, 125.8, 127.3, 128.3, 129.6, 131.5, 132.2, 132.9, 134.3, 138.2, 139.0, 141.0, 143.8, 151.2, 163.2, 164.4, 165.1, and 165.5 (possibly due to overlap, not all the expected resonances are observed); λ_{max}(EtOH)/nm 220, 255sh, 300 and 480, log ε 4.39, 4.26, 4.46 and 3.38.

(*b*) In the same way, the adduct **17b** (0.256 g) and DDQ (0.15 g), heated under reflux in benzene (215 cm^3) for 30 min yielded *tetramethyl* 8-*methyl*-3-*phenylazocino*[2,1,8-cd]*pyrrolizine*-1,2,5,6-*tetracarboxylate* **18b** (0.174 g, 68%) as purple–red prisms (from methanol), m.p. 166–167 °C (lit.,[4] m.p. for putative **16b** 152–164 °C) (Found: M^+, 489.1487); δ_C 23.8, 51.5, 51.9, 52.0, 52.3, 115.5, 117.8, 118.3, 121.1, 125.8, 127.2, 128.4, 129.8, 131.2, 131.5, 138.1, 139.7, 142.1, 146.1, 146.8, 153.2, 163.1, 164.8, 164.9 and 165.6; λ_{max}(EtOH)/nm 220sh, 260, 309 and 498, log ε 4.42, 4.27, 4.51 and 3.25.

Crystal Structure Determination for **7**.—*Crystal Data.* $C_{27}H_{25}NO_8$, $M = 491.46$, triclinic, space group $P\bar{1}$, $a = 7.9462(10)$, $b = 12.2836(23)$, $c = 13.085(3)$ Å, $\alpha = 97.040(17)$, $\beta = 101.551(16)$, $\gamma = 99.326(13)°$, $V = 1219$ Å^3 (from setting angles of 12 reflections with $2\theta = 43$–$50°$, $\bar{\lambda} = 1.5418$ 4 Å), $Z = 2$, $D_{calc} = 1.339$ g cm^{-3}, $T = 298$ K, colourless crystal, $\mu = 0.79$ mm^{-1}, $F(000) = 516$.

Data collection and processing. Stoë STADI-4 four-circle diffractometer, graphite-monochromated Cu-K_α X-radiation, $T = 298$ K, $\omega - 2\theta$ scans using the learnt-profile method,[13] 1972 unique reflections ($2\theta_{max}$ 90°, $h - 7 \rightarrow 7$, $k - 11 \rightarrow 11$, l $0 \rightarrow 11$) measured, giving 1923 with $F \geqslant 6\,\sigma(F)$ for structure solution and refinement. No significant crystal decay or movement was observed.

Structure solution and refinement. Automatic direct methods[14] located all non-H atoms which were then refined (by

least-squares on F[15]) with anisotropic thermal parameters. The phenyl ring was refined with ideal D_{6h} symmetry and H atoms were included at fixed, calculated positions. At final convergence R, R_w = 0.0488, 0.0834 respectively, S = 1.420 for 314 refined parameters and the final ΔF synthesis showed no $\Delta\rho$ above 0.24 e Å^{-3}. The weighting scheme $w^{-1} = \sigma^2(F) + 0.000\,09\,F^2$ gave satisfactory agreement analyses, a secondary extinction parameter refined to 4.78(5) × 10^{-6} and in the final cycle $(\Delta/\sigma)_{max}$ was 0.68. Tables of bond lengths, bond angles and torsion angles have been deposited at the CCDC.*

Crystal Structure Determination for **17a**.—*Crystal data.* $C_{27}H_{25}NO_8$, M = 491.46, monoclinic, space group $P2_1/n$, a = 9.6752(7), b = 24.6574(21), c = 11.4156(9) Å, β = 114.335(16)°, V = 2841 Å^3 [from 2θ values of 70 reflections measured at ±ω (2θ = 23–40°, $\bar{\lambda}$ = 1.541 84 Å)], Z = 4, D_{calc} = 1.315 g cm^{-3}, T = 298 K, deep red needle, 0.02 × 0.08 × 0.68 mm, μ = 0.77 mm^{-1}, F(000) = 1032.

Data collection and processing. Stoë STADI-4 four-circle diffractometer, graphite-monochromated Cu-K_α X-radiation, T = 298 K, $\omega - 2\theta$ scans with ω scan width (1.05 + 0.347 tanθ)°, 4968 reflections measured (2θ_{max} 120°, h −10 → 9, k 0 → 27, l 0 → 12) measured, 3518 unique (R_{int} 0.11), giving 1466 with $F \geqslant 4\sigma(F)$ for structure solution and refinement. Linear isotropic crystal decay (*ca.* 7%) corrected for during data processing.

Structure solution and refinement. Automatic direct methods[14] located all non-H atoms which were then refined (by least-squares on F[15]) with anisotropic thermal parameters. The phenyl ring was refined with ideal D_{6h} symmetry and H atoms were included at fixed, calculated positions. At final convergence R, R_w = 0.0824, 0.0928 respectively, S = 0.988 for 317 refined parameters and the final ΔF synthesis showed no $\Delta\rho$ above 0.35 e Å^{-3}. The weighting scheme $w^{-1} = \sigma^2(F) + 0.001\,28\,F^2$ gave satisfactory agreement analyses, a secondary extinction parameter refined to 2.6(6) × 10^{-7} and in the final cycle $(\Delta/\sigma)_{max}$ was 0.15. Tables of bond lengths, bond angles and torsion angles have been deposited at the CCDC.*

Crystal Structure Determination on **18a**.—*Crystal data.* $C_{27}H_{23}NO_8$, M = 489.5, triclinic, space group $P\bar{1}$, a = 10.596(3), b = 10.642(3), c = 12.906(4) Å, α = 67.288(10), β = 65.809(13), γ = 74.605(10)°, v = 1215 Å^3 [from 2θ values of 52 reflections measured at ±ω(2θ = 27–30°, $\bar{\lambda}$ = 1.541 84 Å)], Z = 2, D_{calc} = 1.338 g cm^{-3}, T = 173 ± 0.3 K, deep red lath, 0.41 × 0.27 × 0.15 mm, μ = 0.79 mm^{-1}, F(000) = 512.

Data collection and processing. Stoë STADI-4 four-circle diffractometer equipped with Oxford Cryosystems low temperature device,[18] graphite-monochromated Cu-K_α X-radiation, T = 173 K, $\omega - 2\theta$ scans with ω scan width (0.66 + 0.347 tanθ)°, 3443 unique data (2θ_{max} 120°, h −10 → 11, k −10 → 11, l 0 → 14), giving 2587 reflections with $F \geqslant 6\sigma(F)$ for use in all calculations. No significant crystal decay or movement was observed.

Structure solution and refinement. Automatic direct methods[14] located all non-H atoms which were then refined (by least-squares on F[15]) with anisotropic thermal parameters. The phenyl rings was refined with idealised D_{6h} symmetry and the H atoms were included at fixed, calculated positions. At final convergence R, R_w = 0.0600, 0.0832 respectively, S = 1.123 for 317 refined parameters and the final ΔF synthesis showed no $\Delta\rho$ above 0.32 e Å^{-3}. The weighting scheme $w^{-1} = \sigma^2(F) + 0.001\,478\,F^2$ gave satisfactory agreement analyses, an isotropic extinction parameter refined to 1.3(3) × 10^{-6} and in the final cycle $(\Delta/\sigma)_{max}$ was 0.012. Atomic scattering factors were inlaid,[15] molecular geometry calculations utilised CALC[16] and illustrations were prepared using ORTEPII.[17] Tables of bond lengths, bond angles and torsion angles have been deposited at the CCDC.*

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* For details of the CCDC deposition scheme see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, 1991, Issue 1.

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