Structurally Modified Antitumour Agents. Part 1. Synthesis of Cyclopropapyrrolo[1,2-*a*]indoles related to Mitosenes by Intramolecular Cycloaddition[1]

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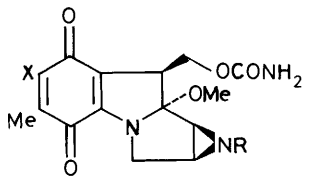
N-Alkylation of indole-2-carbaldehydes with allyl halides followed by reaction with toluene-*p*-sulphonylhydrazide gives tosylhydrazones (**14**). Decomposition of the sodium salts of the tosylhydrazones (**14**) at *ca.* 140 °C results in an intramolecular 1,3-dipolar cycloaddition to give, after loss of nitrogen, the cyclopropapyrroloindoles (**15**). At lower temperatures the intermediate cycloadduct pyrazoline can be isolated. The cyclopropapyrroloindoles react as simple indoles and readily undergo Vilsmeier formylation.

The mitomycins, exemplified by mitomycin C (**1a**) and A (**1b**), are a class of potent antitumour antibiotics.[2] Indeed mitomycin C is a clinically useful chemotherapeutic agent for the treatment of various tumours. Although it has long been known that mitomycins require reductive activation before they can react covalently with DNA and hence exert their cytotoxic action, it is only recently that the details of this activation process, and the subsequent formation of a powerful electrophile that can alkylate and cross-link DNA, have begun to emerge. Much research has gone into establishing the molecular basis for the antitumour action of the mitomycins, and several groups have made valuable contributions, although a significant amount of recent work has come from the laboratories of Danishefsky,[3] Kohn,[4] and Tomasz and Nakanishi.[5] In general, these investigations have been of two types: whereas the Yale group have been concerned with the chemical synthesis and characterisation of the likely intermediates in the 'activation cascade' using *N*-methylmitomycin A (**1c**) as substrate,[3] the groups at Houston[4] and New York[5] have concentrated on the chemical and electrochemical reduction of mitomycin C (**1a**) in the presence of various nucleophiles. These nucleophiles have ranged from simple low molecular weight anions to a double-stranded synthetic copolymer of deoxy-guanylate and -cytidylate and to a bacterial DNA itself. As a result of these studies, the mechanism shown in Scheme 1 has been proposed for the alkylation and cross-linking of DNA by mitomycins.

The initial step in the process is the single electron reduction of the mitomycin (**1**) to the mitomycin semiquinone radical anion (**2**). This is followed by loss of methanol and ring opening of the aziridine to give the electrophilic species (**5**). The fact that all those steps occur at the radical anion stage, and not at the hydroquinone stage as previously thought, now seems beyond doubt.[3c,4f,6] In the chemical reductions, the intermediate mitosene semiquinone (**3**) can reoxidise on exposure to air to give the aziridinomitosene (**4**).[3b,7] Interestingly, such azirdino-mitosenes, for example the compound (**4**; X = OMe, R = Me) derived from *N*-methylmitomycin A (**1c**) (mitomycin F), also exhibit antitumour activity.[8] The activated mitosene semiquinone (**3**) is electrophilic at both C-1 and C-10 by virtue of aziridine ring opening assisted by the radical anion as shown, and elimination of the $OCONH_2$ fragment assisted by the 'push' from the indole nitrogen respectively. However, the first alkylation of DNA is thought to occur at C-1. Evidence for this comes from the isolation, after oxidation, of the mono DNA adduct (**7**). After enzymic digestion of the adduct, a mitosene derivative bound to DNA through the 2-NH_2 group of deoxyguanosine was isolated and characterised.[5d,5g] To date, the alternative



(**1a**) X = NH_2, R = H (mitomycin C)
(**1b**) X = OMe, R = H (mitomycin A)
(**1c**) X = OMe, R = Me (*N*-methylmitomycin A; mitomycin F)

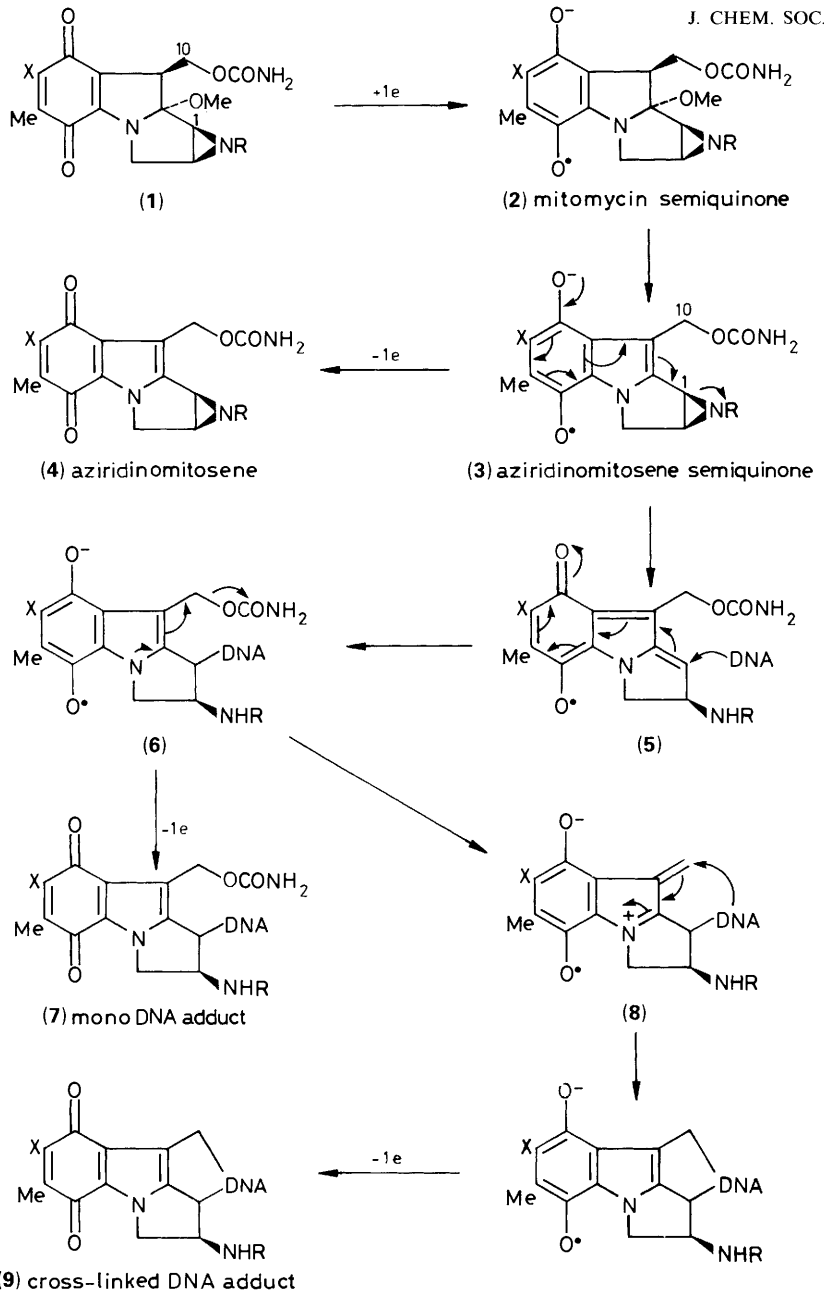
C-10 linked mono-DNA adduct has not been observed. After alkylation at C-1, the reactive electrophilic iminium species (**8**) is formed, which then completes the cross-linking of DNA, and recent efforts have succeeded in isolating and characterising such a cross-linked adduct (**9**).[5e] Further evidence for this mechanism comes from the fact that decarbamoylmitomycin C (**1a**; lacking $CONH_2$ group), a compound that itself possesses significant antibiotic and cytotoxic activity, also alkylates DNA through the C-1 position, but is apparently incapable of forming cross-links to DNA.[5g]

However, in mitomycin derivatives in which the electrophilicity at C-1 is totally removed by prior ring opening of the aziridine, C-10 has been shown to be electrophilic, the results being in accord with the intermediacy of an iminium ion formed by loss of the $OCONH_2$ group assisted by the indole nitrogen, after reductive activation.[4f] Our own work in this area has concentrated on a different approach. Rather than opening the aziridine ring, we decided to investigate the role of C-10 in alkylation processes by preparing compounds in which the electrophilicity at C-1 is much reduced by substituting a cyclopropane for the aziridine ring. Such a compound, for example (**10**), on reductive activation in the presence of a nucleophile followed by oxidative work-up, should yield the C-10 adduct (**11**) (Scheme 2), and if biologically active would open up the possibility for the isolation of the corresponding C-10 linked mono DNA adduct.

This paper reports the full details of our initial studies on the synthesis of such a ring system, the previously unknown cyclopropapyrrolo[1,2-*a*]indole, and the total synthesis and properties of the cyclopropamitosene (**10**; X = OMe) is described in the following paper.[9]

Results and Discussion

The route to the cyclopropapyrrolo[1,2-*a*]indole system is based on the intramolecular 1,3-dipolar cycloaddition of a diazo compound to an alkene double bond.[10] The diazo

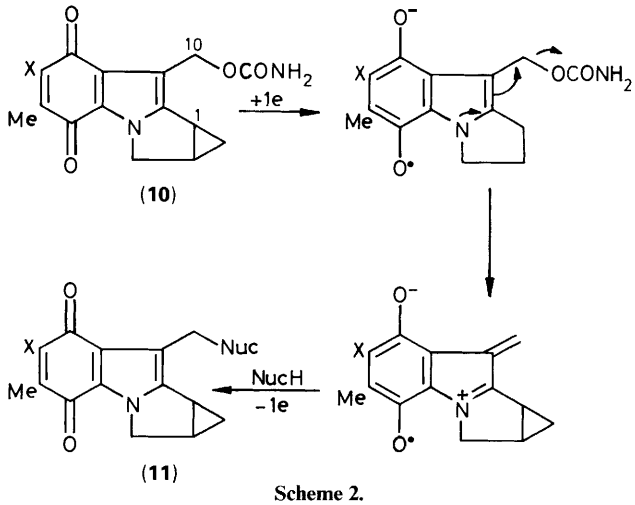


Scheme 1. Proposed mechanism for the activation-alkylation cascade of the mitomycins

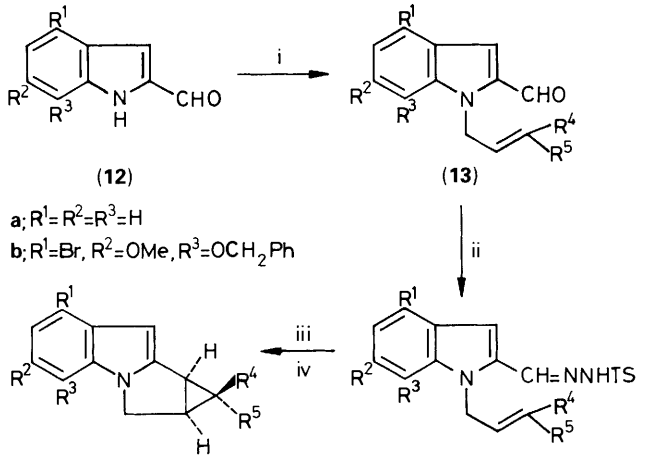
compounds were generated from the sodium salts of the tosylhydrazones (**14**), readily prepared from indole-2-carbaldehyde (**12a**) or 7-benzyloxy-4-bromo-6-methoxyindole-2-carbaldehyde (**12b**)[11] (Scheme 3).

Thus, the indolecarbaldehyde (**12**) was *N*-alkylated by treatment with sodium hydride in *N*,*N*-dimethylformamide (DMF) followed by the appropriate allyl bromide to give the corresponding *N*-allyl derivatives (**13**). Attempted alkylation with cinnamyl bromide and with ethyl 4-bromobut-2-enoate was unsuccessful. The aldehydes (**13**) were converted into their tosylhydrazones by reaction with toluene-*p*-sulphonylhydrazide ($TsNHNH_2$) in methanol. In the case of the compounds derived from indole-2-carbaldehyde and crotyl bromide (1-bromobut-2-ene), ^1H n.m.r. spectroscopy showed that the *N*-crotylindole-2-carbaldehyde (**13b**) was formed as a *ca.* 4:1 mixture of *trans*- and *cis*-isomers. However, after recrystallisation, the corresponding tosylhydrazone (**14b**) was largely the *trans*-isomer.

In order to effect the key intramolecular cycloaddition reaction, the tosylhydrazone (**14a**) was converted into its



Scheme 2.



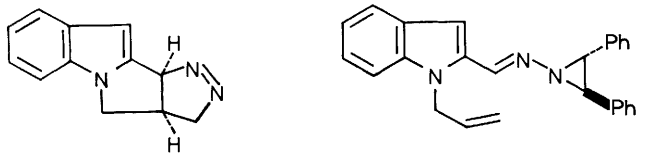
(12) (13) (14) (15)

a; $R^1=R^2=R^3=H$

b; $R^1=Br$, $R^2=OMe$, $R^3=OCH_2Ph$

For (13)–(15)		R^1	R^2	R^3	R^4	R^5
	a	H	H	H	H	H
	b	H	H	H	H	Me
	c	H	H	H	Me	Me
	d	Br	OMe	OCH_2Ph	H	H

Scheme 3. *Reagents:* i, NaH, DMF, $R^4R^5C{=}CHCH_2Br$; ii, $TsNHNH_2$, MeOH; iii, NaH, THF; iv, heat, solvent



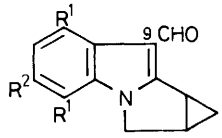
(16) (17)

sodium salt by reaction with sodium hydride in tetrahydrofuran (THF). The salt was collected by filtration, and thermolysed in boiling xylene to give the desired cyclopropapyrroloindole (**15a**) in 43% yield. When the salt was decomposed at a lower temperature in boiling benzene the intermediate [3 + 2] adduct, the pyrazoline (**16**) was isolated (29%). A slightly higher yield (40%) of the pyrazoline (**16**) was obtained when the hydrazone (**17**), derived from *trans*-1-amino-2,3-diphenylaziridine was used as the precursor. Such hydrazones, introduced by Eschenmoser and co-workers,[12] have advantages over other diazo compound precursors in that they are cleaved under mild thermal conditions without the need for added reagents. On further heating in boiling xylene, the cycloadduct (**16**) lost nitrogen to give the cyclopropane (**15a**) in high yield (89%).

Similar results were obtained from the tosylhydrazones (**14b—d**). Thus the *N*-crotyl derivative gave an inseparable mixture of two isomeric cyclopropapyrroloindoles in 47% combined yield on thermolysis of its sodium salt in boiling chlorobenzene. The major compound (*ca.* 3.5:1) was the *exo*-isomer (**15b**) (*cf.* ref. 10*b*), the stereochemistry of which was assigned by nuclear Overhauser effect difference spectroscopy. Pre-irradiation of the methyl signal of the major isomer caused enhancement of the two ring junction proton signals.

Similarly the dimethylcyclopropapyrroloindole (**15c**) was formed in 55% yield from the sodium salt of the tosylhydrazone (**14c**), and the benzene ring substituted derivative (**14d**) gave the corresponding cyclopropane (**15d**) in good yield (72%).

Finally, as a test of their reactivity and stability, the cyclopropapyrroloindoles (**15a**) and (**15d**) were subjected to Vilsmeier formylation conditions, involving reaction with *N*-methylformanilide and phosphorus oxychloride in 1,2-dichloroethane. Both compounds behaved as simple indoles, the cyclopropane ring remaining intact, to give the corresponding 9-formyl derivatives* (**18a**) and (**18b**) in good yield (91% and 73% respectively).



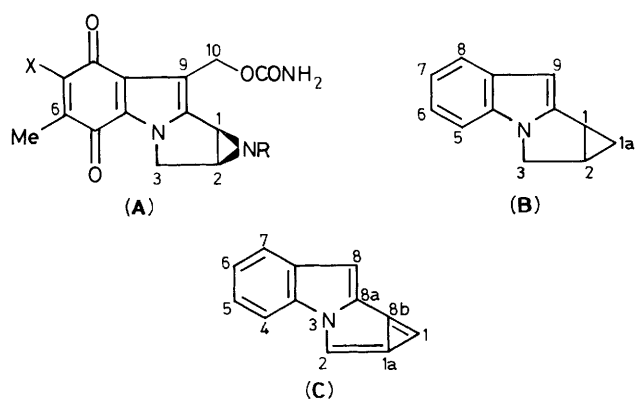
(18)

a; $R^1=R^2=R^3=H$

b; $R^1=Br$, $R^2=OMe$, $R^3=OCH_2Ph$

In conclusion, the intramolecular cycloaddition strategy described herein provides a short route to novel cyclopropapyrroloindoles in which the tetracyclic system is formed in a single step from a relatively simple 1,2-disubstituted indole. However, if such cyclopropane analogues are to be used to probe the biological mechanism of action of the mitomycin antibiotics, a fully and correctly substituted cyclopropapyrroloindole quinone will be required. The total synthesis of such a compound is described in the following paper.

* In the Discussion, in order to facilitate comparison with the mitomycin series of compounds where the 1,2-aziridinomitosene name and numbering (**A**) is universally used (although strictly 1,2-epiminomitosene is more correct, we propose to refer to our novel cyclopropapyrroloindole as a 1,2-cyclopropamitosene and number it accordingly as in (**B**). However in the Experimental section the IUPAC approved name and numbering (**C**) is used for the compounds described.



(A) (B) (C)

Experimental

Light petroleum refers to the fraction boiling in the range 60—80 °C, and was distilled before use. Ethers refers to diethyl ether. Ether and THF were dried by distillation from potassium–benzophenone ketyl. Benzene, toluene, and xylene were dried over sodium wire. DMF was stirred over barium oxide for 12 h at room temperature and then distilled from alumina at reduced pressure to dry it. Chlorobenzene was distilled before use. All distilled solvents were stored over 4 Å molecular sieves under nitrogen. Unless otherwise stated, all other reagents were used as supplied. T.l.c. was carried out using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Plates were visualised under u.v. light and with iodine vapour. For column chromatography, Merck Kieselgel 60 H or Kieselgel 60 (70—230 mesh) was used. I.r. spectra were recorded using a Perkin-Elmer 1710 FT spectrometer. U.v. spectra were

recorded on Pye Unicam SP8-100 spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Bruker AM500 (500 MHz), a JEOL GSX270 (270 MHz), a Bruker WM250 (250 MHz), a Perkin-Elmer R32 (90 MHz), or on a Varian EM360 (60 MHz) spectrometer. ^{13}C N.m.r. spectra were recorded on a Bruker AM500 (125 MHz), or on a Bruker WM250 (62.9) MHz). High and low resolution mass spectra were recorded on a VG Micromass 7070B instrument, in the electron impact mode at 70 eV, using a direct insertion probe, unless otherwise specified.

1-*Allylindole*-2-*carbaldehyde* (**13a**).—To a flask charged with sodium hydride (50%; 0.494 g, 10.3 mmol) was added dry light petroleum (10 ml). The mixture was stirred for 1 min after which the petroleum was removed *via* a syringe, and the flask contents dried under vacuum. Indole-2-carbaldehyde (**12a**) (1.00 g, 6.89 mmol) in DMF (40 ml) was added dropwise, and the mixture was stirred at room temperature for 30 min. Allyl bromide (1.246 g, 10.3 mmol) was added, and the mixture was stirred at room temperature. After 3 h, water (10 ml) was cautiously added, and the mixture was extracted with ether (3 × 100 ml). The combined ethereal extracts were washed with water (2 × 100 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and evaporated to give the *title compound* (**13a**) (1.212 g, 95%) as a colourless oil (Found: C, 77.7; H, 6.1; N, 7.6. $C_{12}H_{11}NO$ requires C, 77.8; H, 6.0; N, 7.6%); $\nu_{max.}$(film) 1 670, 1 610, 1 460, 1 120, 760, and 740 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 9.85 (1 H, s, CHO), 7.75—7.52 (1 H, m, 4-H), 7.38—7.01 (4 H, m, ArH + 3-H), 6.25—5.55 (1 H, m, C*H*=CH_2), 5.20—4.85 (3 H, m, NCH_2 and =C*H*H), and 4.73—4.65 (1 H, m, =C*H*H); *m*/*z* 185 (M^+, 100%), 168 (36), 167 (16), 156 (38), and 89 (22).

1-(*But*-2-*enyl*)*indole*-2-*carbaldehyde* (**13b**).—Following the above procedure, indole-2-carbaldehyde (**12a**) (2.00 g, 13.8 mmol) with sodium hydride (50%; 0.794 g, 16.5 mmol) and 1-bromobut-2-ene (2.234 g, 16.5 mmol) in DMF (80 ml), gave the *title compound* (**13b**) (2.03 g, 74%) as a clear oil, on purification by column chromatography, characterised as a 4:1 mixture of *trans*:*cis* isomers (Found: C, 78.3; H, 6.8; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%); $\nu_{max.}$(film) 1 675, 1 615, 1 520, and 754 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 9.88 (1 H, s, CHO), 7.76—7.1 (1 H, d, *J* 8 Hz, 4-H), 7.43—7.14 (4 H, m, 3-H, 5-H, 6-H, 7-H), 5.58 (2 H, m, CH=CH), 5.27 and 5.12 (2 H, dd, *J* 7, 2 Hz and dd, *J* 7, 2 Hz, NCH_2, *cis*/*trans*), 1.88 and 1.63 (3 H, dd, *J* 7, 1 Hz and dd, *J* 7, 1 Hz, Me, *cis*/*trans*); *m*/*z* 199 (M^+, 100%), 184 (37), 182 (23), 170 (21), 156 (20), 144 (45), 89 (31), and 55 (54).

1-(2-*Methylbut*-2-*enyl*)*indole*-2-*carbaldehyde* (**13c**).—Following the above procedure, indole-2-carbaldehyde (**12a**) (1.00 g, 6.89 mmol) with sodium hydride (50%; 0.40 g, 8.28 mmol) and 4-bromo-2-methylbut-2-ene (0.865 g, 8.28 mmol) in DMF (50 ml), gave the *title compound* (**13c**) (1.22 g, 83%) as a clear oil, on purification by column chromatography (Found: C, 78.9; H, 7.1; N, 6.5. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.1; N, 6.6%); $\nu_{max.}$(film) 1 674, 1 615, 1 415, 1 353, and 754 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 9.89 (1 H, s, CHO), 7.74 (1 H, d, *J* 8 Hz, 4-H), 7.39 (2 H, m, ArH), 7.26 (1 H, s, 3-H), 7.18 (1 H, m, ArH), 5.23 (3 H, s, NCH_2CH), 1.89 (3 H, s, Me), and 1.70 (3 H, s, Me); *m*/*z* 213 (M^+, 77%), 198 (17), 145 (100), 69 (69), and 41 (64).

1-*Allyl*-7-*benzyloxy*-4-*bromo*-6-*methoxyindole*-2-*carbaldehyde* (**13d**).—Following the above procedure, 7-benzyloxy-4-bromo-6-methoxyindole-2-carbaldehyde (**12b**) (1.0 g 2.7 mmol) with sodium hydride (50%; 0.160 g, 3.3 mmol) and allyl bromide (0.403 g, 3.3 mmol) in DMF (50 ml) gave the *title compound* (**13d**) (1.05 g, 97%) as a pale yellow oil on purification by column chromatography (Found: C, 60.3; H, 4.75; N, 3.75. $C_{20}H_{18}BrNO_3$ requires C, 60.0; H, 4.5; N, 3.5%); $\nu_{max.}$(CCl_4) 1 680, 1 620, 1 500, 1 260, and 700 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 9.78 (1 H, s, CHO), 7.41 (5 H, m, ArH), 7.24 (1 H, s, 5-H), 7.13 (1 H, s, 3-H), 5.90 (1 H, m, C*H*=CH_2), 5.40 (2 H, m, NCH_2), 5.11 (2 H, s, OCH_2), 5.00 (1 H, dd, *J* 10, 1 Hz, =C*H*H), 4.65 (1 H, dd, *J* 14, 1 Hz, =C*H*H), and 3.95 (3 H, s, OMe); *m*/*z* 401/399 (M^+, 10%), 310/308 (45), 186 (16), and 91 (100).

1-*Allylindole*-2-*carbaldehyde Tosylhydrazone* (**14a**).—1-Allylindole-2-carbaldehyde (**13a**) (0.414 g, 2.24 mmol) was added to a stirred solution of toluene-*p*-sulphonylhydrazide (0.458 g, 2.46 mmol) in methanol (2.0 ml). The mixture was stirred at room temperature for 3 h, after which water (1.0 ml) was added, and the resulting precipitate filtered off. Recrystallisation (methanol–water) of the latter gave the *title compound* (**14a**) (0.727 g, 92%) as colourless crystals, m.p. 125—127 °C (decomp.) (Found: C, 64.6; H, 5.4; N, 11.8. $C_{19}H_{19}N_3O_2S$ requires C, 64.6; H, 5.4; N, 11.9%); $\nu_{max.}$(Nujol) 3 200, 1 610, 1 320, 1 160, and 740 cm^{-1}; δ_H(60 MHz; $CDCl_3$) 8.1 (1 H, br, NH), 8.0—7.9 (2 H, d, *J* 8 Hz, ArH), 7.65—7.46 (1 H, m, 4-H), 7.40—7.18 (6 H, m, ArH), 6.71 (1 H, s, CH=N), 6.10—5.6 (1 H, m, C*H*=CH_2), 5.18—4.82 (3 H, m, NCH_2, =C*H*H), 4.7—4.62 (1 H, m, =CH*H*), and 2.41 (3 H, s, ArMe); *m*/*z* 353 (M^+, 11%), 183 (5), 169 (75), 168 (100), 154 (19), 91 (4), and 28 (43).

1-(*But*-2-*enyl*)*indole*-2-*carbaldehyde Tosylhydrazone* (**14b**).—Following the above procedure 1-(but-2-enyl)indole-2-carbaldehyde (**13b**) (0.2 g, 1.0 mmol) with toluene-*p*-sulphonylhydrazide (0.224 g, 1.2 mmol) in methanol (2 ml) gave the *title compound* (**14b**) (0.338 g, 92%) as colourless crystals, m.p. 94—95 °C (Found: C, 65.3; H, 5.7; N, 11.7. $C_{20}H_{21}N_3O_2S$ requires C, 65.4; H, 5.8; N, 11.4%); $\nu_{max.}$(Nujol) 3 200, 1 608, 1 598, 1 168, and 940 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.89 (1 H, s, NH), 7.84 (2 H, d, *J* 7 Hz, ArH), 7.71—7.58 (5 H, m, ArH), 7.30 (2 H, d, *J* 7 Hz, ArH), 6.70 (1 H, s, CH=N), 5.45 (2 H, d, *J* 5 Hz, *HC*=C*H*), 5.03 (2 H, s, NCH_2), 2.43 (3 H, s, ArMe), and 1.59 (3 H, s, Me); *m*/*z* 367 (M^+; 6%), 339 (7), 211 (5), and 183 (100).

1-(2-*Methylbut*-2-*enyl*)*indole*-2-*carbaldehyde Tosylhydrazone* (**14c**).—Following the above procedure, 1-(2-methylbut-2-enyl)indole-2-carbaldehyde (**13c**) (0.448 g, 2.103 mmol) with toluene-*p*-sulphonylhydrazide (0.469 g, 2.55 mmol) in methanol (5 ml) gave the *title compound* (**14c**) (0.697 g, 87%) as a colourless crystalline solid, m.p. 121—122 °C (decomp.) (Found: C, 66.0; H, 6.1; N, 10.4. $C_{21}H_{23}N_3O_2S$ requires C, 66.1; H, 6.1: N, 11.0%); $\nu_{max.}$(CCl_4) 3 200, 1 600, 1 360, 1 160, 1 050, and 660 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.83 (2 H, m, ArH), 7.63 (1 H, s, NH), 7.56 (1 H, d, *J* 8 Hz, 4-H), 7.25 (5 H, m, ArH + 3-H), 7.07 (1 H, m, ArH), 6.68 (1 H, s, CH=N), 5.09 (3 H, s, NCH_2CH), 2.40 (3 H, s, ArMe), 1.86 (3 H, s, Me), and 1.68 (3 H, s, Me); *m*/*z* 381 (M^+, 0.1%), 353 (8), 246 (5), 198 (100), 154 (22), and 91 (71).

1-*Allyl*-7-*benzyloxy*-4-*bromo*-6-*methoxyindole*-2-*carbaldehyde Tosylhydrazone* (**14d**).—Following the above procedure 1-allyl-7-benzyloxy-4-bromo-6-methoxyindole-2-carbaldehyde (**13d**) (0.720 g, 1.8 mmol) and toluene-*p*-sulphonylhydrazide (0.368 g, 1.98 mmol) in methanol (4 ml) gave the *title compound* (**14d**) (0.828 g, 81%) as colourless crystals, m.p. 54—55 °C (decomp.) (Found: C, 57.1; H, 4.7; N, 7.1. $C_{27}H_{26}BrN_3O_4S$ requires C, 57.0; H, 4.6; N, 7.4%); $\nu_{max.}$(Nujol) 3 181, 1 605, 1 500, and 1 167 cm^{-1}; δ_H(250 MHz; CD_3COCD_3) 10.20 (1 H, s, NH), 8.01 (1 H, s, 5-H), 7.81 (2 H, d, *J* 8 Hz, ArH), 7.58—7.34 (7 H, m, ArH), 7.14 (1 H, s, 3-H), 6.69 (1 H, s, C*H*=N), 5.79 (1 H, m, C*H*=CH_2), 5.34 (2 H, m, NCH_2), 5.12 (2 H, s, OCH_2), 4.87 (1 H, d, *J* 15 Hz, =C*H*H), 4.49 (1 H, d, *J* 17 Hz, =CH*H*), 3.93 (3 H, s, OMe), and 2.39 (3 H, s, ArMe); *m*/*z* 541/539 (M^+ − 28, 3%), 450/448 (9), 385/383 (16), and 91 (100).

1-*Allyl*-2-(2,3-*diphenylaziridin*-2-*yliminomethyl*)*indole* (**17**).—1-Amino-2,3-diphenylaziridine[12] (97 mg, 0.542 mmol) was

added to a solution of 1-allylindole-2-carbaldehyde (**13a**) in ether (3 ml), and the mixture was stirred at 0 °C for 12 h. The solvent was removed under reduced pressure and the residue purified by chromatography on Florisil, eluting with ether–light petroleum to give the *title compound* (**17**) (0.103 g, 52%) as a colourless solid, m.p. 123—124 °C (Found: C, 82.6; H, 6.3; N, 11.1. $C_{26}H_{23}N_3$ requires C, 82.7; H, 6.1; N, 11.1%); $\nu_{max.}$($CHCl_3$) 1 580, 900, 740, and 650 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.87 (1 H, s, CH=N), 7.72—7.09 (14 H, m, ArH), 7.03 (1 H, s, 3-H), 5.71—5.55 (1 H, m, C*H*=CH_2), 4.93 (1 H, d, *J* 9 Hz, =C*H*H), 4.61—4.45 (3 H, m, NCH_2, and =CH*H*), 4.06 (1 H, d, *J*, 3 Hz, aziridine CH), and 3.84 (1 H, d, *J*, 3 Hz, aziridine CH); *m/z* 377 (M^+, 0.3%), 349 (0.5), 180 (100), 168 (54), 89 (21), and 28 (65).

3,3a,4,10b-*Tetrahydropyrazolo*[3′,4′:3,4]*pyrrolo*[1,2-a]*indole* (**16**).—(a) *From* 1-*Allylindole-2-carbaldehyde tosylhydrazone* (**14a**). Sodium hydride (50%; 0.040 g, 0.83 mmol) was added to a stirred solution of 1-allylindole-2-carbaldehyde tosylhydrazone (**14a**) (0.20 g, 0.56 mmol) in dry THF (5 ml). After 10 min, the precipitate was filtered off, washed with THF (2 × 5 ml), and then dried. The dry solid was suspended in dry benzene (20 ml), and the solution heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was purified by chromatography eluting with ethyl acetate–light petroleum to give the *title compound* (**16**) (0.032 g, 29%) as a colourless solid, m.p. 159—161 °C (Found: M^+, 197.0956. $C_{12}H_{11}N_3$ requires 197.0953); $\nu_{max.}$(Nujol) 1 480, 1 220, 770, 750, and 745 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.65 (1 H, d, *J* 8 Hz, ArH), 7.18—7.05 (3 H, m, ArH), 6.65 (1 H, s, 10-H), 6.10 (1 H, d, *J* 9 Hz, 10b-H), 4.75 (2 H, m, 4-CH_2), 4.32 (1 H, t, *J*, 10 Hz, 3-C*H*H), 3.72 (1 H, m, 3-C*H*H), and 3.49 (1 H, m, 3a-H); *m/z* 197 (M^+, 37%), 169 (70), 168 (100), 154 (41), and 28 (43).

(b) *From* 1-*allyl*-2-(2,3-*diphenylaziridin*-2-*yliminomethyl*)-*indole* (**17**). The imine (**17**) (0.050 g, 0.133 mmol) was dissolved in dry benzene (30 ml) and the solution refluxed for 3 h. Removal of solvent under reduced pressure followed by purification of the residue by chromatography gave the *title compound* (**16**) (0.0104 g, 40%) identical with the previous sample.

1,1a,2,8b-*Tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole* (**15a**).—(a) *From* 3,3a,4,10b-*Tetrahydropyrazolo*[3′,4′:3,4]*pyrrolo*[1,2-a]*indole* (**16**). A solution of (**16**) (0.030 g, 0.152 mmol) in dry xylene (5 ml) was refluxed for 4 h. Removal of solvent under reduced pressure followed by chromatography of the residue eluting with ether–light petroleum, gave the *title compound* (**15a**) (0.023 g, 89%) as a colourless solid, m.p. 49—51 °C (Found: C, 84.9; H, 6.7; N, 8.1. $C_{12}H_{11}N$ requires C, 85.2; H, 6.6; N, 8.3%); $\nu_{max.}$(CCl_4) 1 570, 1 455, 1 305, and 1 155 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.52 (1 H, d, *J* 7 Hz, ArH), 7.18—7.01 (3 H, m, ArH), 6.19 (1 H, s, 9-H), 4.11 (2 H, m, 3-CH_2), 2.42 (2 H, m, 1-H, 2-H), 1.29 (1 H, m, 1a-C*H*H), and 0.66 (1 H, q, *J* 4 Hz, 1a-CH*H*); δ_C(125 MHz; $CDCl_3$) 146.55 (s), 133.08 (s), 133.06 (s), 120.30 (d), 120.26(d), 119.07 (d), 108.87 (d), 92.08 (d), 46.42 (t), 21.31 (d), 17.28 (t), and 15.70 (d); *m/z* 169 (M^+, 87%), 168 (100), and 154 (32) (Found: M^+, 169.0892. $C_{12}H_{11}N$ requires 169.0891).

(b) *From* 1-*allylindole*-2-*carbaldehyde tosylhydrazone* (**14a**). The procedure was followed as for the formation of (**16**), but using xylene (150 ml) instead of benzene for the thermolysis stage. Accordingly, 1-allylindole-2-carbaldehyde tosylhydrazone (**14a**) (1.63 g, 4.62 mmol), gave the *title compound* (**15a**) (0.335 g, 43%), identical with the above sample.

2-*Methyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]-*indole* (**15b**).—Sodium hydride (50%; 0.045 g, 0.94 mmol) was added to a solution of 1-(but-2-enyl)indole-2-carbaldehyde tosylhydrazone (**14b**) (0.227 g, 0.619 mmol) in THF (7 ml). After the mixture had been stirred for 15 min, the precipitate was filtered off, washed with THF (20 ml), and dried. The dry solid was suspended in chlorobenzene (70 ml) and then plunged into a Woods' metal-bath at 220 °C. The mixture was refluxed for 3 h after which the solvent was removed under reduced pressure to give a pale yellow oil. Purification by chromatography gave the *title compound* (**15b**) (0.053 g, 47%) as a colourless solid, m.p. 44—45 °C; characterised as a 3.4:1 mixture of *exo*:*endo* isomers (Found: M^+, 183.1062. $C_{13}H_{13}N$ requires 183.1048); $\nu_{max.}$-(CCl_4) 1 580, 1 450, 1 310, and 1 160 cm^{-1}; δ_H(250 MHz; CD_3COCD_3) 7.39 (1 H, m, 7-H), 7.14—6.87 (3 H, m, 4-H, 5-H, 6-H), 6.15 and 6.08 (1 H, s, 8-H), 4.24—3.91 (2 H, m, 2-CH_2), 2.61—2.37 and 2.24—2.13 (2 H, m, 8b-H, 1a-H), 1.45 and 0.95 (1 H, m, 1-CH), 1.16 and 0.59 (3 H, d, *J* 5 Hz, Me); *m/z* 183 (M^+, 100%), 182 (44), 168 (63), 167 (42), 154 (37), and 83 (28).

1,1-*Dimethyl*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*-[1,2-a]*indole* (**15c**).—Following the above procedure, 1-(2-methylbut-2-enyl)indole-2-carbaldehyde tosylhydrazone (**14c**) (0.305 g, 0.800 mmol) with sodium hydride (50%; 0.060 g, 1.2 mmol) in THF (10 ml) followed by refluxing in dry chlorobenzene (80 ml) gave the *title compound* (**15c**) (0.087 g, 55%) as a pale yellow solid, m.p. 93—95 °C (Found: M^+, 197.1201. $C_{14}H_{15}N$ requires 197.1204); $\nu_{max.}$(CCl_4) 1 610, 1 460, 1 380, and 1 305 cm^{-1}; δ_H(250 MHz; CD_3COCD_3) 7.42 (1 H, d, *J* 7 Hz, 7-H), 7.15 (1 H, d, *J* 7 Hz, 4-H), 7.00 (2 H, m, 5-H, 6-H), 6.14 (1 H, s, 8-H), 4.13 and 3.88 (2 H, m, 2-CH_2), 2.32 (1 H, d, *J* 8 Hz, 8b-H), 2.14 (1 H, m, 1a-H), 1.19 (3 H, s, Me), and 0.62 (3 H, s, Me); *m/z* 197 (M^+, 50%), 182 (40), 167 (25), and 154 (100).

6-*Benzyloxy*-7-*bromo*-5-*methoxy*-1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole* (**15d**).—1-Allyl-7-benzyloxy-4-bromo-6-methoxyindole-2-carbaldehyde tosylhydrazone (**14d**) (0.517 g, 0.91 mmol) was stirred with sodium hydride (58%; 0.065 g, 1.36 mmol) in THF (15 ml). After 15 min, the solution was filtered, and the filtrate concentrated under reduced pressure to give a beige solid. This was dissolved in chlorobenzene (100 ml) and the solution refluxed for 2 h. Removal of solvent under reduced pressure followed by chromatography of the residue gave the *title compound* (**15d**) (0.250 g, 72%) as a colourless solid, m.p. 110 °C (Found: C, 62.2; H, 4.7, N, 3.5. $C_{20}H_{18}BrNO_2$ requires C, 62.5; H, 4.7; N, 3.7%); $\nu_{max.}$(CCl_4) 1 500, 1 290, 1 260, 1 170, 1 130, and 700 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 7.39 (5 H, m, ArH), 6.91 (1 H, s, 6-H), 6.07 (1 H, s, 8-H), 5.09 (2 H, s, OCH_2), 4.03 (2 H, m, 2-CH_2), 3.89 (3 H, s, MeO), 2.33 (1 H, m, 8b-H), 2.21 (1 H, m, 1a-H), 1.19 (1 H, m, 1-C*H*H), and 0.51 (1 H, m, 1-CH*H*); *m/z* 385/383 (M^+, 5%), 294/292 (14), 188 (29), 125 (42), 111 (66), 97 (83), 91 (79), 83 (63), 71 (65), 57 (100), and 43 (79).

1,1a,2,8b-*Tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole*-8-*carbaldehyde* (**18a**).—*N*-Methylformanilide (0.043 g, 0.318 mmol) and phosphorus oxychloride (0.049 g, 0.318 mmol) were stirred under a calcium oxide drying tube for 15 min. The resulting precipitate was cooled to 0 °C, for the addition of 1,2-dichloroethane (2 ml). The cyclopropapyrrolo[1,2-*a*]indole (**15a**) (0.0456 g, 0.27 mmol) was added, and the mixture was heated to 40 °C for 3 h. Aqueous sodium acetate (1M; 1 ml) was added, and the mixture was extracted with ethyl acetate (2 × 10 ml). The combined extracts were washed with water (2 × 10 ml) and brine (1 × 5 ml), dried ($MgSO_4$), and evaporated to give a pale yellow solid. Purification by chromatography eluting with ether–light petroleum gave the *title compound* (**18a**) (0.048 g, 91%) as a colourless solid, m.p. 144—145 °C (Found: C, 79.2; H, 5.5; N, 7.15. $C_{13}H_{11}NO$ requires C, 79.2; H, 5.6; N, 7.1%); $\nu_{max.}$($CHCl_3$) 1 641, 1 550, 1 395, and 1 040 cm^{-1}; δ_H(250 MHz;

$CDCl_3$) 10.09 (1 H, s, CHO), 8.18 (1 H, d, *J* 8 Hz, ArH), 7.29—7.11 (3 H, m, ArH), 4.18 (2 H, m, 2-CH_2), 2.83 (1 H, m, 8b-H), 2.54 (1 H, m, 1a-H), 1.50 (1 H, m, 1-C*H*H), and 0.80 (1 H, m, 1-CH*H*); *m/z* 197 (M^+, 90%), 196 (100), 168 (30), 167 (38), 149 (97), 135 (81), and 106 (72); Found: M^+, 197.0837. $C_{13}H_{11}NO$ requires 197.0841.

*7-Benzyloxy-7-bromo-5-methoxy-*1,1a,2,8b-*tetrahydrocyclopropa*[3,4]*pyrrolo*[1,2-a]*indole-8-carbaldehyde* (**18b**).—Following the above procedure *N*-methylformanilide (0.049 g, 0.366 mmol), phosphorus oxychloride (0.056 g, 0.366 mmol), and the cyclopropapyrrolo[1,2-*a*]indole (**15d**) (0.117 g, 0.31 mmol) in 1,2-dichloroethane (2 ml) gave the *title compound* (**18b**) (0.092 g 73%) as a colourless solid, m.p. 131—133 °C (Found: M^+, 411.0475. $C_{21}H_{18}BrNO_3$ requires 411.0470); $\nu_{max.}$(CCl_4) 1 700, 1 480, 1 020, and 930 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 10.77 (1 H, s, CHO), 7.43—7.12 (5 H, m, ArH), 7.08 (1 H, s, 6-H), 5.13 (2 H, s, OCH_2), 4.01 (2 H, m, 2-CH_2), 3.90 (3 H, s, OMe), 2.96 (1 H, m, 8b-H), 2.31 (1 H, m, 1a-H), 1.40 (1 H, m, 1-C*H*H), and 0.51 (1 H, m, 1-CH*H*); *m/z* 413/411 (M^+, 9%), 322/320 (22), 240 (6), 135 (87), and 106 (100).

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