Structurally Modified Antitumour Agents. Synthesis of a Cyclopropamitosene

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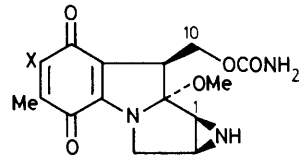
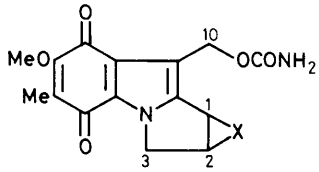
The cyclopropapyrrolo[1,2-*a*]indolequinone (**3**), the cyclopropane analogue of a biologically active aziridinomitosene derived from mitomycin A, has been synthesised from the benzaldehyde (**4**).

The mitomycins, exemplified by mitomycins A and C (**1**, X = OMe and NH_2 respectively), are useful antitumour agents which act by covalent binding to DNA. The details of this binding process, which is thought to involve *in vivo* reductive activation to give a species capable of cross-linking DNA by acting as a bis-electrophile at C-1 and C-10, have been intensively investigated of late by several research groups.[1] Structurally related aziridinomitosenes, such as the *N*-methylaziridinomitosene (**2**) derived from mitomycin A (**1**, X = OMe), are also biologically active since they too have the potential to act as bis-electrophiles,[2] and indeed such mitosenes lacking the 9a-methoxy group, or the semiquinones derived therefrom, may be important intermediates in the biological activation process. Our own work in this area is designed to focus attention on the role of C-10 in the alkylation of DNA, by the preparation of compounds in which the electrophilicity at C-1 is much reduced by replacing the readily opened aziridine ring by a less reactive cyclopropane, and we now report the total synthesis of such a compound, the cyclopropapyrroloindolequinone (**3**), the cyclopropane analogue of the mitosene derived from mitomycin A.

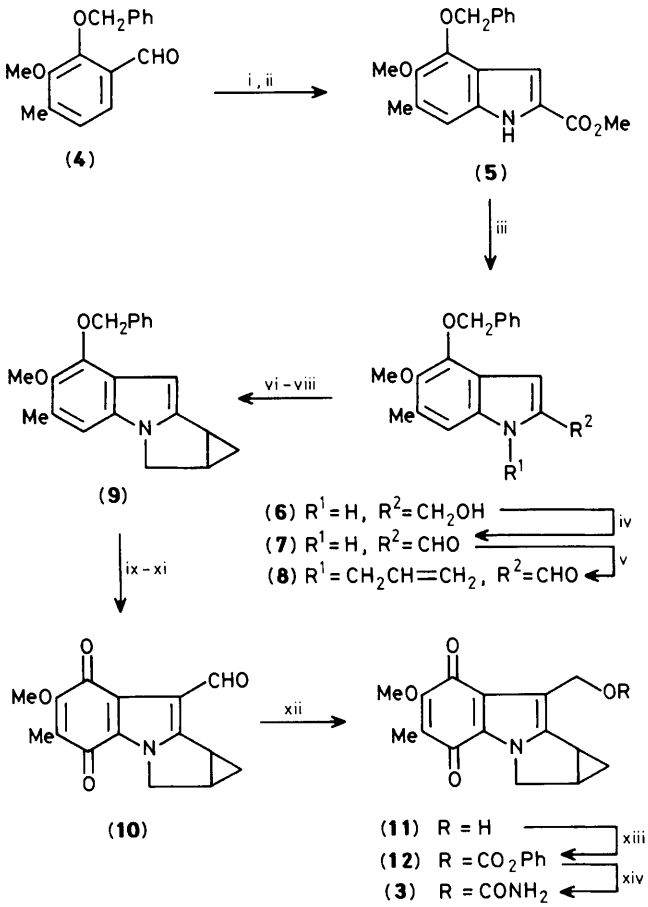
The overall strategy involves, as key steps, the high yielding preparation of a polysubstituted indole from a relatively simple benzaldehyde,[3] followed by an intramolecular cycloaddition reaction[4] which, in contrast to much synthetic work in the mitosene area which leads only to tricyclic derivatives, gives the tetracyclic ring system *directly* from an indole. The starting material for the synthesis is 4-methylsalicyclic acid, which is commercially available, and was converted into 2-benzyloxy-3-methoxy-4-methylbenzaldehyde (**4**)† in 26% overall yield by standard chemistry: esterification (MeOH, H^+) (97%), 3-formylation ($MeOCHCl_2$, $TiCl_4$, CH_2Cl_2, 0 °C) (76%), *O*-benzylation ($PhCH_2Br$, NaH, DMF) (78%), Baeyer–Villiger oxidation of the 3-formyl group and hydrolysis of the resulting formate ester (*m*-$ClC_6H_4CO_3H$, CH_2Cl_2 then aq. HCl, MeOH) (95%), *O*-methylation (Me_2SO_4, K_2CO_3, acetone) (71%), and conversion of the ester to aldehyde ($LiAlH_4$, ether, then $BaMnO_4$, CH_2Cl_2) (67%). The aldehyde (**4**) was condensed with methyl azidoacetate in methanol in the presence of sodium methoxide, and the resulting vinyl azide was decomposed in boiling xylene to give the 4,5,6-trisubstituted indole-2-ester (**5**), m.p. 151—152 °C, in 77% over the two steps (Scheme 1). The ester (**5**) was converted into the key indole precursor for the intramolecular cycloaddition reaction, the *N*-allylindole-2-carbaldehyde (**8**),



(**1**)



(**2**) X = NMe
(**3**) X = CH_2



(**4**) (**5**) (**9**)

Scheme 1. *Reagents*: i, $MeO_2CCH_2N_3$, NaOMe, MeOH, −15 °C; ii, xylene, reflux; iii, $LiAlH_4$, ether; iv, $BaMnO_4$, CH_2Cl_2; v, NaH, allyl bromide, dimethyl formamide (DMF); vi, *p*-$MeC_6H_4SO_2NHNH_2$, MeOH; vii, NaH, tetrahydrofuran (THF); viii, PhCl, reflux; ix, NMFA, $POCl_3$, $ClCH_2CH_2Cl$, heat; x, H_2, 10% Pd–C, EtOAc; xi, Fremy's salt, NaH_2PO_4, acetone; xii, $NaBH_4$, MeOH, $FeCl_3$ work-up; xiii, $ClCO_2Ph$, pyridine, 0 °C; xiv, NH_3, CH_2Cl_2, −78 °C.

† Satisfactory spectroscopic data, and microanalyses or high resolution mass spectra were obtained for all new compounds.

by reduction to the alcohol (**6**) (99%), reoxidation to the aldehyde (**7**) (69%), and allylation (80%). Reaction of the aldehyde (**8**) with 4-toluenesulphonylhydrazide gave the corresponding tosylhydrazone (77%), which was converted into its sodium salt, and heated in boiling chlorobenzene to give the tetracyclic cyclopropapyrrolo[1,2-*a*]indole (**9**) in 84% yield. The C-10 side chain was introduced by formylation (63%) using *N*-methylformanilide (NFMA) and phosphorus oxide trichloride, and the resulting aldehyde was debenzylated (99%), and oxidised with Fremy's salt (75%) to give the tetracyclic quinone (**10**), m.p. 184—185 °C. The synthesis was completed by elaboration of the C-10 side chain by reduction to the alcohol (**11**) (98%), conversion into the carbonate (**12**) (72%), and finally into the required urethane (**3**) (79%).

The cyclopropane analogue (**3**) is an orange, crystalline solid, m.p. 190—191 °C, $\lambda_{max.}$ (MeOH) 236 (log ε 4.32), 288 (4.06), 343 (3.40), and 465 nm (3.17); $\nu_{max.}$ ($CHCl_3$) 3610, 3450, 1730, 1660, 1640, and 1605 cm^{-1}; δ (250 MHz; $CDCl_3$) 0.55 (1 H, m), 1.31 (1 H, m), 1.92 (3 H, s, Me), 2.33 (1 H, m, H-2), 2.53 (1 H, m, H-1), 3.99 (3 H, s, OMe), 4.26 (2 H, m, 3-CH_2), 4.61 (2 H, br., NH_2), and 5.27 (2 H, AB, *J* 12.5 Hz, 10-CH_2); *m/z* (70 eV; 200 °C) 316 (M^+, 31%), 273 (100), and 256 (47). Since the reduction of the quinone moiety is important in the biological action of mitomycins and mitosenes, we determined the reduction potential of our novel analogue (**3**). This was measured in DMF solution using cyclic voltammetry and found to be −0.399 V, a value which closely matches that reported (−0.390 V) for the *N*-methylaziridinomitosene (**2**).[2a] The biological evaluation of the cyclopropamitosene (**3**) is in hand.

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