A One-step Synthesis of an Aziridino Mitosene Analogue from 2-(*N*-Phenylformimidoyl)indole

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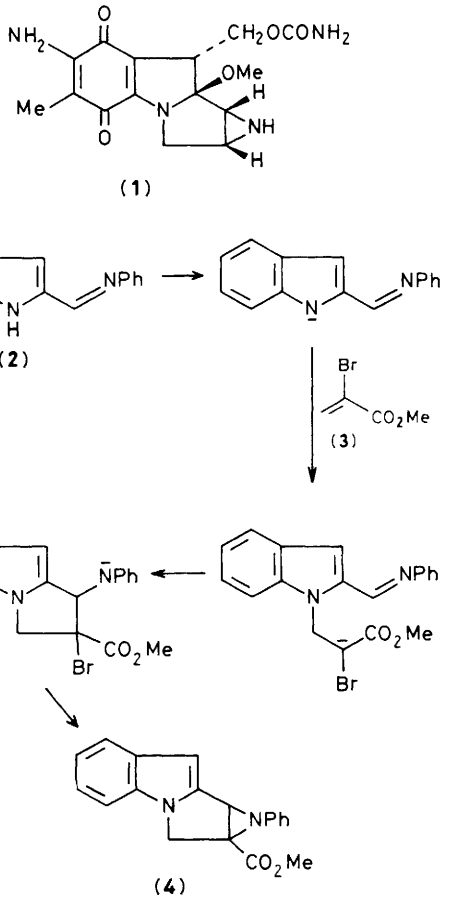
1,1a,2,8b-Tetrahydro-1-phenyl-1a-(methoxycarbonyl)azirino[2',3': 3,4]pyrrolo[1,2-*a*]indole (**4**), containing the complete ring system of the mitomycin antitumour antibiotics, is formed in a single step from 2-(*N*-phenylformimidoyl)indole (**2**) by treatment of its sodium salt with methyl 2-bromopropenoate; the aziridine undergoes facile *thermal* ring-opening to an azomethine ylide which adds *in situ* to dimethyl butynedioate in 1,3-dipolar fashion.

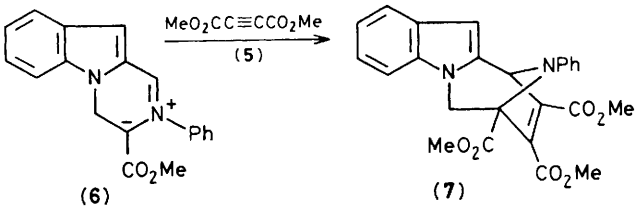
Mitomycin C (**1**), the most important and useful member of the mitomycin class of antitumour antibiotics, is employed clinically in the treatment of a wide variety of cancers in spite of its relatively high toxicity.[1] The remarkable total synthesis of this compound and its congeners by Kishi and coworkers remains the only successful effort in this area,[2] and most work by others has concentrated on the preparation of analogues in the hope of developing a system with a higher therapeutic index.[1,3] As part of a programme directed toward the synthesis of the mitomycins and their analogues, we have discovered a facile route to the mitomycin ring system which involves a one-step bicycloannulation[4] of a 2-imidoyl indole, forming rings C and D in a single operation.

Our strategy is based upon the bicycloannulation reactions reported by White[5] and McIntosh[6] in which an α-chloro acrylic ester or nitrile undergoes conjugate addition by anionic species where the anionic centre is separated by one or two carbons from a ketone or aldehyde group, followed by an intramolecular Darzens reaction with the carbonyl moiety to give a bicyclic epoxide. By analogy, replacement of the carbonyl with an imine group should give a bicyclic aziridine, since the Darzens condensation has previously been applied to the synthesis of aziridines from imines.[7] Accordingly, we proposed that the reaction of a 2-imidoyl indole, *e.g.* (**2**), in the presence of a base, with an α-halogeno acrylic ester, *e.g.* (**3**) would provide the mitomycin ring system in a single synthetic step (four mechanistic steps) as shown in Scheme 1.

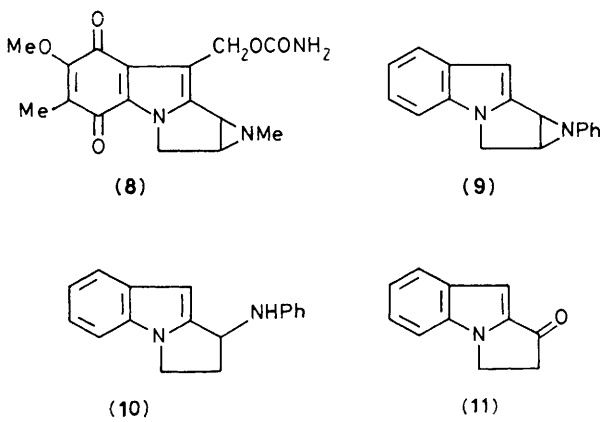
In the event, treatment of 2-(*N*-phenylformimidoyl)indole (**2**) with sodium hydride in tetrahydrofuran, followed by addition of methyl 2-bromopropenoate (**3**) in the presence of hexamethylphosphoric triamide at 0 °C gave, after chromatographic purification, a 60% yield of compound (**4**) [m.p. 118 °C, decomp.; ^{1}H n.m.r. (100 MHz), δ 3.80 (3H, s), 4.25 (1H, d, *J* 12 Hz), 4.35 (1H, s), 4.55 (1H, d, *J* 12 Hz), and 6.55 (1H, s)]. When this aziridine was heated with dimethyl butynedioate (**5**) at 110 °C in diphenyl ether, it underwent smooth ring opening to the azomethine ylide (**6**) (Scheme 2), which was trapped[7b,8] by the acetylene to give quantitatively the 1,3-dipolar addition product (**7**) [m.p. 175.5—177 °C; ^{1}H n.m.r. (100 MHz), δ 3.80 (6H, s), 3.95 (3H, s), 4.45 (1H, d, *J* 12 Hz), 4.75 (1H, d, *J* 12 Hz), 5.85 (1H, s), and 6.55 (1H, s)]. The success of this formally disallowed thermal ring opening is undoubtedly due to the stabilization of the positive and negative charges in (**6**) by the indole nucleus and the ester group, respectively. An analogous thermal ring opening



Scheme 1. Bicycloannulation.



Scheme 2. 1,3-Dipolar cycloaddition.



of a bicyclic aziridine and trapping with (**5**) has been reported by Lown and Matsumoto.[9]

The azirino mitosenes, *e.g.* (**8**), although they were obtained as degradation products in the earliest investigations of the mitomycins[10] and have been found to possess high antitumour activity,[1f,3b] have not been studied extensively owing to the difficulty in synthesizing this important class of mitomycin analogues.[1c] Furthermore, only two previous synthetic pathways to azirinopyrrolo[1,2-*a*]indoles have been reported.[11] Thus, the above described approach to these compounds may open up an efficient route to what has heretofore been an almost inaccessible type of potential antitumour agent.

Efforts to synthesise compound (**9**), by allowing CH_2=$CHPPh_3Br$ to react with (**2**) in a two-phase system in the presence of 50% NaOH (aq.), were not successful. Instead, compound (**10**) [the structure was confirmed by preparation of the authentic compound from (**11**)][12,13] was obtained in low yield. The mechanism of this reaction is, as yet, unknown.[14–16]

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