A Synthesis of the Tetracyclic Nucleus of Mitomycin

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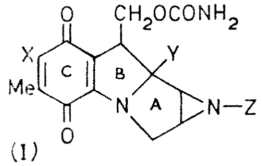
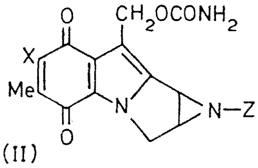
Summary A direct synthesis of a mitomycin-like structure is reported.

THE mitomycins (I) and the aziridinomitosenes (II) are a class of antibiotics with a broad spectrum of antibacterial and antitumour activity.[1] A synthesis of a model aziridinopyrroloindole framework (III) has recently been reported.[2] We describe our synthesis of a model ring system using the readily available 9*H*-pyrrolo[1,2-*a*]indole (IV) as a starting material.[3] Singlet-oxygen oxidation of (IV) in a pyridine–tetrahydrofuran–water solvent affords 3*H*-pyrrolo[1,2-*a*]indole-3-one (V) in 71% yield,[4] n.m.r. (CDCl$_3$) δ 5·95 (upfield half of an AB quartet, *J* 5·5 Hz, 2-H), 6·31 (s, 9-H), 6·90—7·45 (aromatics and low-field half of AB quartet), 7·67 (unique aromatic proton at C-5); i.r. (CHCl$_3$) 5·82 μm., u.v. (EtOH) 355 nm. (ϵ 10,800). The reaction presumably proceeds *via* an endoperoxide intermediate. In contrast to our previous experience with cycloaddition of azides to 3*H*-pyrrolo[1,2-*a*]indoles,[5] addition of phenyl azide to (V) to form triazoline (VI) (56%) was readily accomplished,[6] n.m.r. (CDCl$_3$) δ 5·61 and 6·01 (AB quartet, *J* 10·0 Hz, 1-H and 2-H), 6·64 (s, 9-H); i.r. (CHCl$_3$) 5·73 μm. Photo-elimination of nitrogen from (VI), using a sunlamp with a plate-glass filter, afforded the desired tetracyclic aziridine derivative (VII) (100%) yield of material nearly identical with the analytical sample,[†] m.p. 133—135°, 40% from (IV); n.m.r. (CDCl$_3$) δ 3·82 and 4·02 (AB quartet, *J* 3·7 Hz, 1-H and 2-H), 6·64 (s, 9-H); i.r. (CHCl$_3$) 5·75 μm. When the chemical shifts of the aziridine protons in (VII) are compared to data in the Table, it can be seen that the


(I)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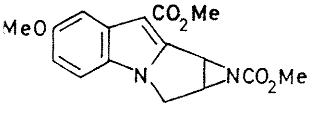
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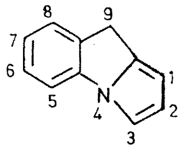
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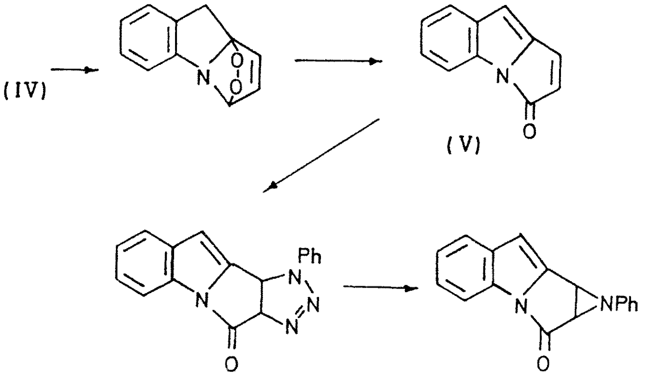


[†] All new compounds gave satisfactory elemental analyses.

result is within the limits to be expected for our substitution pattern. Also, when the J_{cis} value for the protons at the aziridine ring junction of (VII) is compared with that for mitomycin (I) (Table) one concludes that the J value for (VII) is consistent for an *N*-phenylmitomycin analogue. The diminution in J_{cis} upon fusion of the aziridine to five membered rings in (I) and (VII) as compared to (VIII), (IX), (X), and (XI) are parallel to the observed effects with epoxides and episulphides.[7] The enhancement of J_{cis} for (III) is without precedent.

N.m.r. data for aziridines

Compound	Solvent	δ	J_{cis}
(I)[a]	$CDCl_3$–C_6D_6	2·87	4·5
(II)[a]	$CDCl_3$	3·25	—
(III)	$CDCl_3$–$(CD_3)_2SO$	5·66, 5·80	7·7
(VII)	$CDCl_3$	3·80, 4·02	3·7
(VIII[b])	neat	3·0	6·6
(IX)[c]	neat	3·30	6·3
(X)[d]	CCl_4	3·1	6·0
(XI)[e]	$CDCl_3$	4·06	6·5

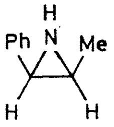
[a] G. Morton, Lederle Laboratories Division, American Cyanamid Co., personal communication, data for (I), X = Y = OMe, Z = H, data for (II), X = OMe, Z = Me, δ midpoint of multiplet.

[b] S. Brois and L. Beardsley, *Tetrahedron Letters*, 1966, 5116, δ for benzylic H.

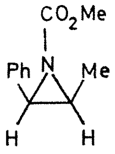
[c] S. Brois, Esso Research Laboratories, personal communication, δ for benzylic H.

[d] J. Deyrup and R. Greenwald, *J. Amer. Chem. Soc.*, 1965, **87**, 4538, δ for benzylic H.

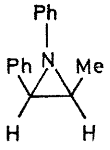
[e] A. E. Pohland, R. C. Badger, and N. H. Cromwell, *Tetrahedron Letters*, 1965, 4639, δ midpoint of multiplet.



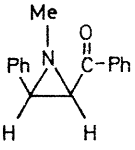
(VIII)



(IX)



(X)



(XI)

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[1] (a) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, D. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *J. Amer. Chem. Soc.*, 1962, **84**, 3187; (b) J. B. Patrick, R. P. Williams, W. E. Meyer, W. Fulmor, D. B. Cosulich, R. W. Broschard, and J. S. Webb, *ibid.*, 1964, **86**, 1889.

[2] T. Hirata, Y. Yamada, and M. Matsui, *Tetrahedron Letters*, 1969, **19**.

[3] V. J. Mazzola, K. F. Bernady, and R. W. Franck, *J. Org. Chem.*, 1967, **32**, 486.

[4] (a) P. de Mayo and S. T. Reid, *Chem. and Ind.*, 1962, 1576; (b) E. Hoft, A. R. Katritzky, and M. R. Nesbit, *Tetrahedron Letters*, 1968, 2028 and 1969, 3041; (c) H. H. Wasserman and A. H. Miller, *Chem. Comm.*, 1969, 199.

[5] R. W. Franck and K. F. Bernady, *J. Org. Chem.*, 1968, **33**, 3050.

[6] P. Scheiner, *J. Org. Chem.*, 1965, **30**, 7.

[7] K. Tori, T. Komeno, and T. Nakagawa, 1964, **29**, 1137.