Cyclopropapyrrolo[1,2-*a*]indoles

Graham B. Jones and Christopher J. Moody*

Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, U.K.

Decomposition of the tosylhydrazones (**3**), prepared from indole-2-carbaldehyde in two steps, gives the cyclopropapyrrolo[1,2-*a*]indoles (**4**), novel analogues of the mitomycin antitumour antibiotics, by an intramolecular cycloaddition reaction.

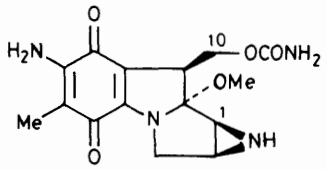
The mitomycins are a class of potent antitumour antibiotics, among which mitomycin C (**1**) is a clinically useful chemotherapeutic agent. The closely related, but structurally simpler mitosenes, for example the *N*-methylaziridinomitosene (**2**), also exhibit antitumour activity. However, mitomycins themselves are biologically inactive, requiring *in vivo* activation, and recently considerable effort has been devoted to the identification of the intermediates involved in this reductive activation process.[1,2] The suitably activated mitomycin is a powerful bis-electrophile, and acts as an alkylating and cross-linking agent for DNA by reaction at C-1 and/or C-10, although attack by nucleic acids has been demonstrated chemically only at C-1, *i.e.* with ring opening of the aziridine.[3] As part of our work on mitomycins and their analogues, 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. We now describe our preliminary results on the synthesis of such a ring system, the previously unknown cyclopropapyrrolo[1,2-*a*]indole (**4**).

The route to cyclopropapyrroloindoles (**4**) is based on the intramolecular 1,3-dipolar cycloaddition of a diazo compound to an alkene double bond.[4] The precursors for the cycloaddition reaction were the tosylhydrazones (**3**), prepared from indole-2-carbaldehyde by *N*-alkylation with the appropriate allyl halide, followed by condensation with toluene-4-sulphonylhydrazide ($TsNHNH_2$) (Scheme 1).

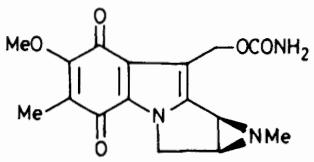
Thermolysis of the sodium salt of the tosylhydrazone (**3a**),† formed by reaction with sodium hydride in tetrahydrofuran (THF), in boiling xylene gave the cyclopropapyrroloindole (**4a**)‡ (43%) directly. When the sodium salt was decomposed at a lower temperature in boiling benzene the intermediate [3+2] cycloadduct (**5**), formed from the corresponding diazo compound, was isolated (29%). A slightly higher yield (40%) of the cycloadduct (**5**) was obtained when the hydrazone (**6**), derived from 1-amino-2,3-diphenylaziridine,[5] was used as the precursor. On heating in boiling xylene, the cycloadduct (**5**)

† Satisfactory spectroscopic and analytical data were obtained for all new compounds.

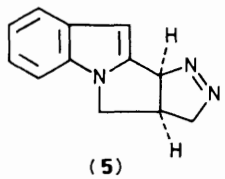
‡ Compound (**4a**), m.p. 49—51 °C, δ_H (250 MHz; $CDCl_3$) 0.66 (1 H, q, *J* 4 Hz), 1.29 (1 H, m), 2.42 (2 H, m), 4.11 (2 H, m), 6.19 (1 H, s), 7.01—7.18 (3 H, m), and 7.52 (1 H, d, *J* 7 Hz); δ_c (125 MHz; $CDCl_3$) 15.7 (d), 17.3 (t), 21.3 (d), 46.4 (t), 92.1 (d), 108.9 (d), 119.1 (d), 120.26 (d), 120.30 (d), 133.06 (s), 133.08 (s), and 146.5 (s).



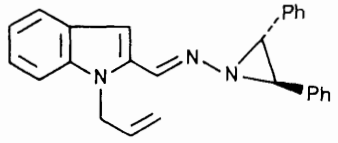
(1)



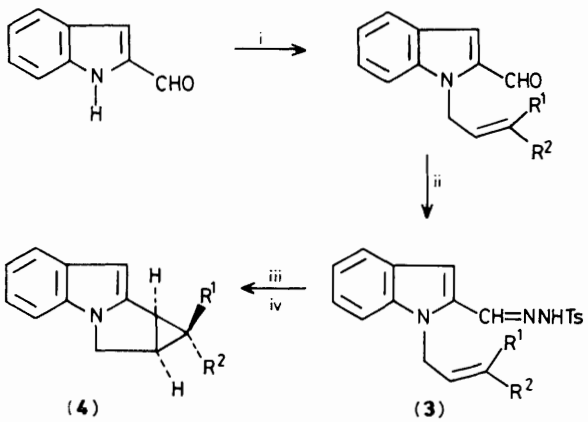
(2)



(5)



(6)



(4) (3)

a, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = Me$
c, $R^1 = R^2 = Me$

Scheme 1. *Reagents:* i, NaH, DMF, $R^1R^2C{=}CHCH_2Br$; ii, $TsNHNH_2$, MeOH; iii, NaH, THF; iv, heat, solvent (see text).

lost nitrogen and gave the cyclopropane (**4a**) (89%). The C-10 carbon was introduced into the cyclopropapyrroloindole nucleus (**4a**) in 90% yield by Vilsmeier formylation.

Similar results were obtained with the tosylhydrazones (**3b**) and (**3c**). Thus the hydrazone (**3b**) [>80% (*E*)-geometry in the crotyl group by ^1H n.m.r. spectroscopy] gave a mixture of two isomeric cyclopropapyrroloindoles (47%), of which the *exo*-isomer (**4b**) (stereochemistry assigned by nuclear Overhauser effect difference spectroscopy) was the major component (*ca.* 3.5 : 1), on treatment with sodium hydride followed by thermolysis in chlorobenzene. Similarly, the dimethylcyclopropapyrroloindole (**4c**) was formed (55%) from the sodium salt of the tosylhydrazone (**3c**).

The intramolecular cycloaddition strategy described herein represents a simple and short route to novel cyclopropane analogues of the mitomycin ring system, which will be of value in probing the biological mechanism of action of the antibiotics. To this end, the synthesis of the cyclopropane analogue of mitosene (**2**) is underway.

We thank the Cancer Research Campaign for a studentship (to G. B. J.), and the Royal Society of Chemistry for a Hickinbottom Fellowship (to C. J. M.).

Received, 20th October 1987; Com. 1525

References

1 S. Danishefsky and M. Ciufolini, *J. Am. Chem. Soc.*, 1984, **106**, 6424; S. J. Danishefsky and M. Egbertson, *ibid.*, 1986, **108**, 4648; M. Egbertson and S. J. Danishefsky, *ibid.*, 1987, **109**, 2204; M. Egbertson, S. J. Danishefsky, and G. Schulte, *J. Org. Chem.*, 1987, **52**, 4424.
2 P. A. Andrews, S. Pan, and N. R. Bachur, *J. Am. Chem. Soc.*, 1986, **108**, 4158; N. Zein and H. Kohn, *ibid.*, 1986, **108**, 296; 1987, **109**, 1576.
3 M. Tomasz, R. Lipman, G. L. Verdine, and K. Nakanishi, *J. Am. Chem. Soc.*, 1985, **107**, 6120.
4 A. Padwa, in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, vol. 2, 1984, Wiley Interscience, New York, p. 277.
5 D. Felix, R. K. Muller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, 1972, **55**, 1276.