The Intramolecular Nitrile Oxide Cycloaddition Approach to the Mitomycins

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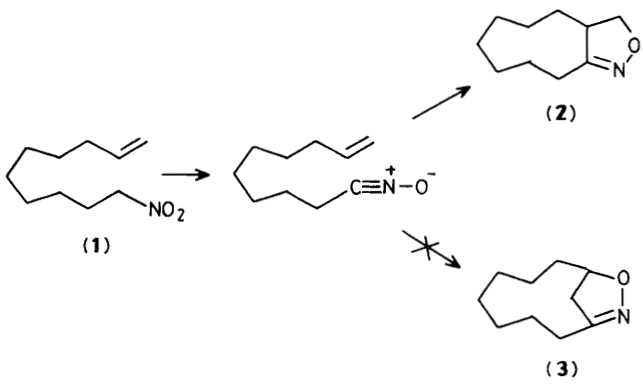
The construction of a benzazocine intermediate by the intramolecular nitrile oxide cycloaddition process has been examined as a possible approach to the mitomycins.

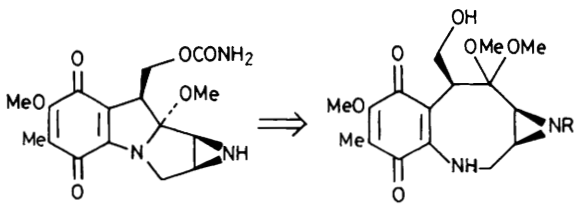
The mitomycins are an important class of quinoid compounds exhibiting potent antibiotic as well as antitumour properties.[1] The mitomycins contain a pyrrolo[1,2-*a*]indole ring system which serves as an important element in the bioreductive activation process leading to the cross-linking of DNA.[2] The first successful total synthesis of the mitomycins A and C was completed more than a decade ago by Kishi through employment of the well precedented transannular cyclization of a 1-benzazocin-5-one.[3]

In exploring the use of the intramolecular nitrile oxide cycloaddition (INOC) reaction in medium-ring synthesis, we decided to examine the possibility of applying such chemistry to the construction of a simple benzazocine, thus providing potentially a new entry to the mitomycins.

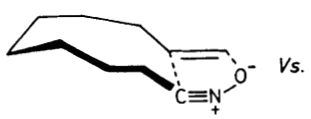
Observations in our own laboratories, as well as those of Asaoka,[4] had revealed that none of the 'normal' 5-substituted isoxazoline will be formed when a medium-sized ring is being generated by the INOC process. Hence, the nitrodecene (**1**) gives rise to only the nine-membered carbocycle (**2**) upon reaction with phenyl isocyanate. None of the ten-membered ring compound (**3**) resulting from the 'normal' intermolecular cycloaddition mode could be detected. Ring strain as well as transannular steric effects thus combine to outweigh the normal regiochemical directing effects provided by the matching of HOMO–LUMO interactions.[5]

Accordingly, it appeared likely that the benzazocine (**5**) and

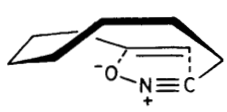




Mitomycin A

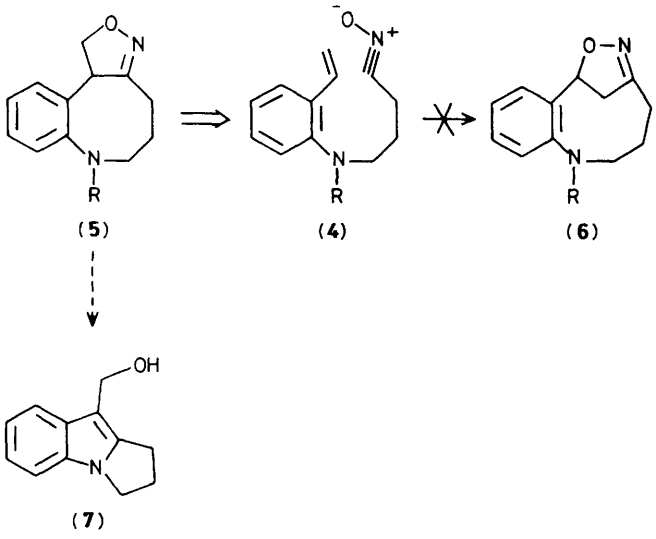


Observed regiochemistry

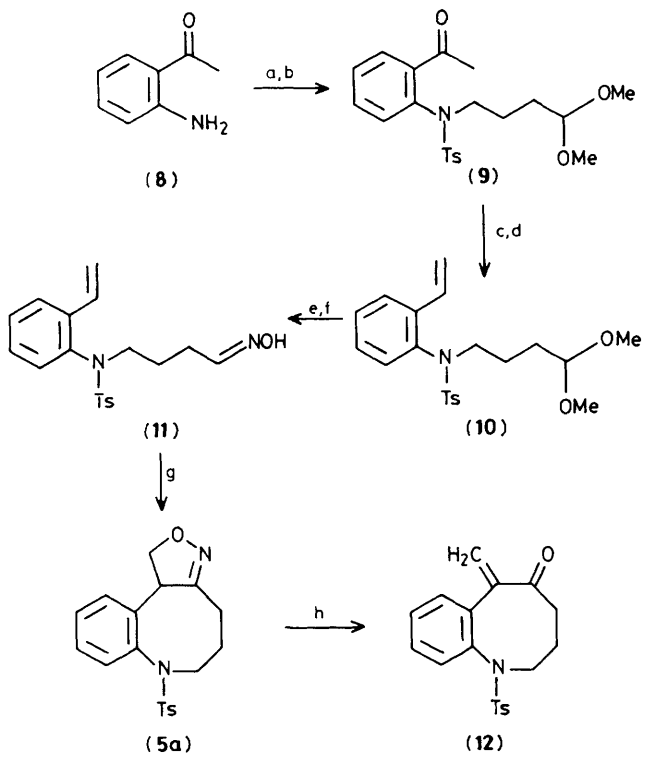


Normal (intermolecular) regiochemistry

Scheme 1. INOC reaction of 10-nitrodec-1-ene (**1**).



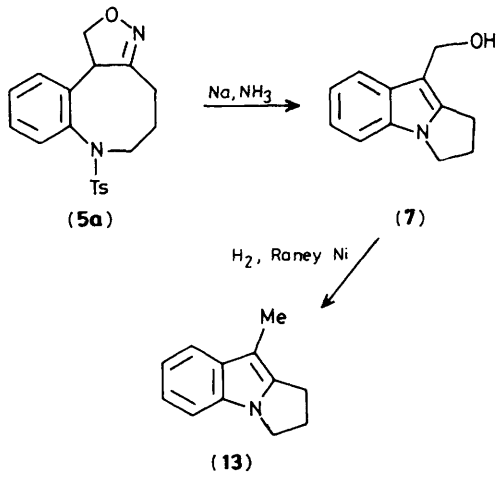
Scheme 2



Scheme 3. *Reagents and conditions*: (a) TsCl, pyridine, DMAP (86%); (b) Bu^{n}Li: $Br(CH_2)_3CH(OMe)_2$, THF/hexamethylphosphoric triamide (46%); (c) $NaBH_4$, EtOH (73%); (d) $MeSO_2Cl$, pyridine, DMAP (55%); (e) 1 M HCl; (f) $H_2NOH{\cdot}HCl$, NaOAc, MeOH [80% from (**10**)]; (g) NaOCl, Et_3N (45%); (h) H_2, Raney Ni, MeOH (81%).

not compound (**6**) would be generated from the nitrile oxide intermediate (**4**) (Scheme 2).

The oxime precursor to the nitrile oxide (**4**) required to test this strategy was prepared from *o*-aminoacetophenone (**8**) as shown in Scheme 3. The amino ketone (**8**) was simply sulphonylated, and then *N*-alkylated with 4-bromobutyraldehyde dimethyl acetal. The ketone group of (**9**) was reduced with sodium borohydride to afford the alcohol as a white solid (m.p. 100 °C). This alcohol underwent smooth dehydration when heated at 60 °C with methanesulphonyl chloride in pyridine containing a catalytic amount of 4-dimethylaminopyridine (DMAP).[6] The dimethyl acetal group was cleaved using 1 M aqueous HCl in tetrahydrofuran (THF), and the resulting aldehyde was treated with excess of hydroxylamine hydrochloride and sodium acetate in methanol to provide a good yield of the oxime (**11**) as a 1 : 1 mixture of the *E*- and *Z*-isomers.

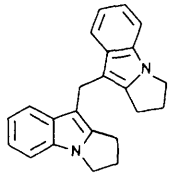


The *E*–*Z*-mixture of oximes was diluted in a large excess of methylene chloride, a catalytic amount of triethylamine was added, and 5.25% aqueous sodium hypochlorite was added slowly.[7] The resulting biphasic mixture was stirred vigorously for 12 h. A 45% isolated yield of the isoxazoline (**5a**) was obtained after silica gel chromatography. Crystallization of this isoxazoline from methylene chloride gave well formed cubic crystals.

Initial attempts to cleave the *N*-tosyl group of (**5a**) by use of basic hydrolysis conditions proved unrewarding. Hydrogenation of the isoxazoline ring of (**5a**) gave rise to the enone (**12**) *via* presumably N–O bond cleavage followed by dehydration.

Finally, the *N*-tosyl protected material (**5a**) was subjected to the sodium–ammonia conditions developed by Lown and Itoh for tosyl group cleavage in a related benzazocine system.[8] These conditions sufficed to remove the *N*-tosyl group as well as to cleave the N–O bond of the isoxazoline ring, for upon work-up followed by silica gel chromatography and recrystallization, well formed crystals of the hydroxymethylindole (**7**) were obtained in 74% yield.† Hydrogenation of (**7**) over

† A solution of compound (**7**) was found to undergo further transformation on standing at room temperature for several hours. The ultimate product of this transformation was identified as the di-indolyl-methane (i):[9] $\nu_{max.}$ (CH_2Cl_2) 3617, 3053, 2978, 2929, 2897, 1461, 1422, 1274, 1256, and 1048 cm^{-1}; ^1H n.m.r. ($CDCl_3$; 300 MHz) δ 7.52 (d, 2H, *J* 7.5 Hz), 7.53—7.00 (m, 6H), 4.13 (s, 2H), 4.00 (t, 4H, *J* 6.9 Hz), 2.64 (t, 4H, *J* 7.2 Hz), and 2.52—2.40 (m, 4H); *m/z* (70 eV), 326 (M^+), 169, 156, 141, 105, 97, 91, and 85. For a mechanism for formation of (i), see ref. 8.



Raney nickel provided the previously known methyl substituted indole (**13**) whose ^{1}H n.m.r. spectrum was identical to that reported by Bailey *et al.*[10]

The present work illustrates the potential for use of the INOC reaction in the construction of the mitomycins.‡

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7 G. A. Lee, *Synthesis*, 1982, 508. The INOC reaction of the oxime derivative containing an *N*-acetyl group in place of the *N*-tosyl group of (**11**) was also examined. The yield of this cycloaddition was lower (34%) than that obtained for (**11**).

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‡ All compounds reported herein exhibited satisfactory i.r., n.m.r., and high resolution mass spectral analysis. The structure of compound (**7**) was further verified by *X*-ray analysis. Full details will be published elsewhere.