

Synthesis and Reactivity of a Novel Oxazolo[2,3-*c*][1,4]benzodiazepine Ring System with DNA Recognition Potential: a New Class of Anthramycins

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The new carbinolamine-containing oxazolo[2,3-*c*][1,4]benzodiazepine ring system has been synthesized, and its reactivity and stability have been compared with properties of the analogous pyrrolo[2,1-*c*][1,4]benzodiazepine system found in the DNA-binding anthramycin antitumour antibiotics.

Recently there has been interest in modifying and extending the recognition patterns of DNA-binding ligands towards GC-selectivity,¹ as the 5'-flanks of some oncogenes are GC-rich and many successful anticancer drugs are GC-selective.² Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) antitumour antibiotics bind covalently to the N-2 of guanine at purine-guanine-purine sites in the minor groove of DNA.³ Modelling studies have suggested that replacement of the C(1) methylene of the PBD skeleton (**1**) with an oxygen should modify binding affinity and sequence selectivity.⁴ However, the oxazolo[2,3-*c*][1,4]benzodiazepine (OBD) ring system (**2**) could not be obtained through synthetic routes established for PBDs⁵ involving direct coupling of substituted benzoyl chlorides (*A*-rings) to intact pyrrolidine derivatives (*C*-rings), as *N*-unsubstituted oxazolidines are unstable under these conditions. We report here, synthesis of the previously unknown OBD ring system by a novel route involving concerted oxazolidine (*C*)-ring formation and attachment (by *N*-benzoylation) of the *A*-ring fragment, followed by steps leading to ring closure. In parallel with the PBD ring system, an N(10)-C(11) carbinolamine (**7**) (crucial for biological

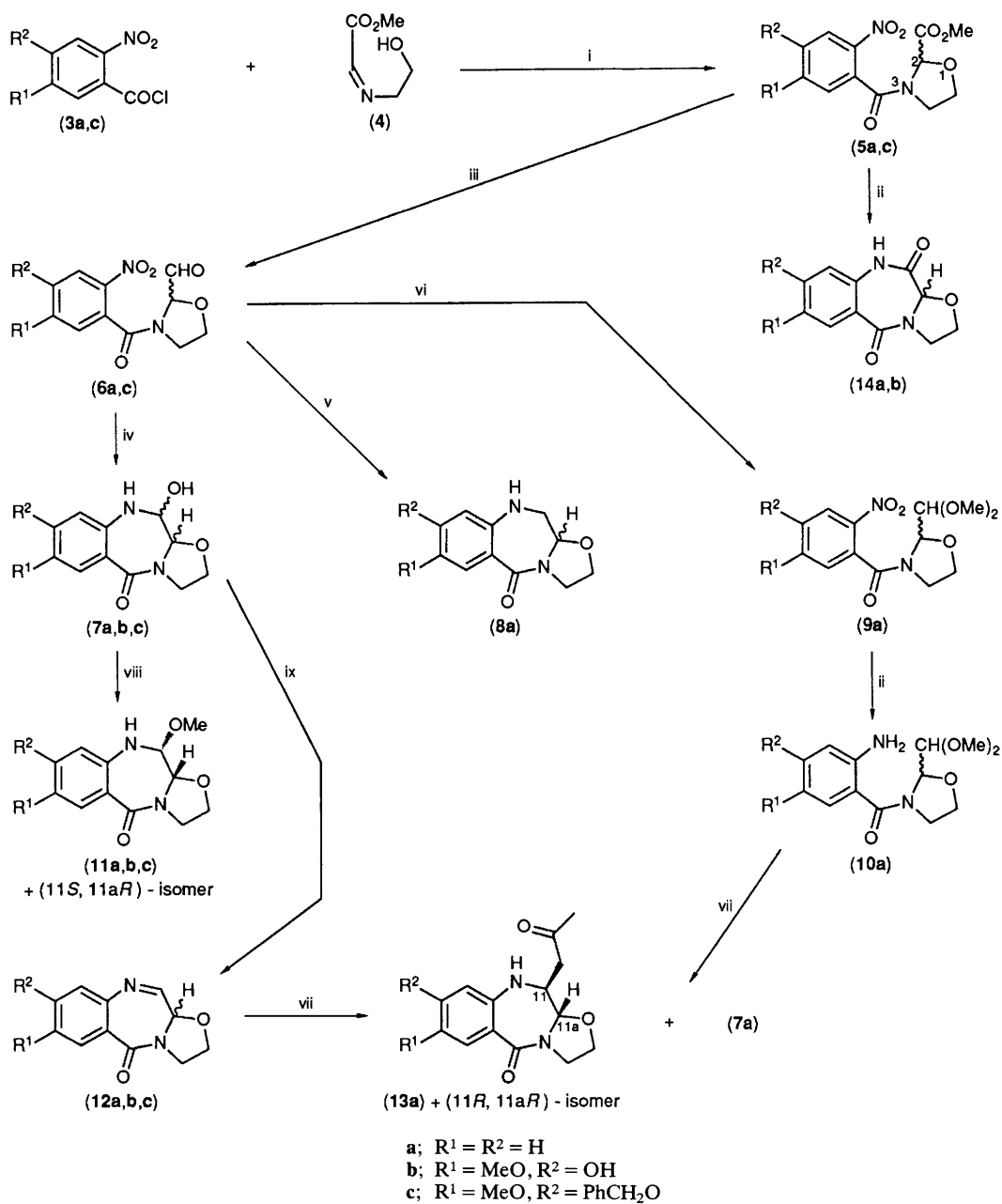
activity) could be obtained and converted to the carbinolamine methyl ether (**11**) or imine (**12**) forms.

Methyl glyoxalate was condensed with ethanolamine (CH₂Cl₂, room temp., molecular sieves) to afford the imino alcohol (**4**) which was treated directly with substituted 2-nitrobenzoyl chlorides (**3a,c**) to afford *N*-(2-nitrobenzoyl)oxazolidine esters of type (**5**) (40–70% yields), each compound existing as a mixture of two rotamers. Reduction with di-isobutylaluminium hydride afforded the corresponding aldehydes of type (**6**) which, unlike pyrrolidine-2-aldehydes, existed mainly in the hydrated form owing to the electron-withdrawing effect of the *C*-ring oxygen. Aldehyde signals were absent (IR) or diminished (¹H NMR) and hydrate CH(OH)₂ signals were observed by ¹H NMR spectroscopy.

Reductive cyclization of aldehydes of type (**6**) under mild conditions (H₂, 10% Pd-C, MeOH, 15 min, room temp., or



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Scheme 1. Reagents: i, pyridine, CH_2Cl_2 , $0^\circ C$, 20 min; ii, 10% Pd-C, H_2 , atm. press., MeOH, 30 min; iii, Bu_2AlH , toluene, $-78^\circ C$, 30 min; iv, 10% Pd-C, H_2 , atm. press., MeOH, 15 min, or $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 90 min; v, 10% Pd-C, H_2 , atm. press., MeOH, 72 h; vi, $(MeO)_3CH$, Dowex 50X resin, CH_2Cl_2 ; vii, acetone-water (8:2), Dowex 50H resin, 60 min; viii, MeOH, reflux, 120 min; ix, $CHCl_3$, reflux, 30 min.

$SnCl_2 \cdot 2H_2O$, MeOH, reflux, 90 min) gave the OBD-carbinolamines (7) in approximately 80% yield. A significant feature of these compounds is the reversal of relative chemical shifts of the C(11) and C(11a) protons [C(11): δ 4.7–4.9; C(11a): δ 5.2–5.45] compared with the PBD system [C(11): 4.35–4.8; C(11a): 3.8–4.2], presumably resulting from the deshielding effect of the C-ring oxygen. In contrast to the PBDs, methyl ether formation occurred stereospecifically to give the (11R,11aS) and (11S,11aR) forms which appeared as one species by NMR spectroscopy, suggesting a mixture of enantiomers with the C(11) and C(11a) protons in the *cis*-configuration. D_2O exchange resulted in disappearance of the N(10)–H doublet (δ ca. 5.3) and collapse of the C(11)

doublet to a singlet, indicating a lack of coupling between the C(11) and C(11a) protons characteristic of *cis*-isomers.⁵ In the PBD system with fixed (*S*) stereochemistry at C(11a), two diastereoisomeric species are frequently observed by NMR spectroscopy owing to the presence of C(11) epimers.

Greater stability of OBD- compared to PBD-carbinolamines is suggested by their resistance to over-reduction (*via* imine intermediates) to the amines (8). Unlike PBDs,⁵ the OBD-carbinolamines can withstand prolonged hydrogenation (*e.g.* up to 72 h at room temp.). In addition, molecular ions were observed in the mass spectra (EI) for all OBD species, contrasting with the PBD system in which a molecular ion is rarely observed for the carbinolamine or methyl ether forms.

An alternative synthetic route involved conversion of the aldehydes to their corresponding dimethyl acetals (**9**), followed by hydrogenation to the amino acetals (**10**). Stirring (**10a**) in acetone-water (8:2) with Dowex 50H resin gave a mixture of the carbinolamine (**7a**) and an unusual addition product, characterised as the C(11)-oxopropyl adduct (**13a**).[‡] In contrast to the OBD-carbinolamines (**7**), the coupling between the C(11) and C(11a) protons indicated a *trans*-arrangement,⁵ suggesting that the C(11)-oxopropyl adduct exists as a mixture of (11*S*,11a*S*)- and (11*R*,11a*R*)-enantiomers. Quantitative conversion of the imine (**12a**) to the oxopropyl adduct (**13a**) could also be achieved under the same reaction conditions. This stereospecific reaction of a carbon nucleophile at C(11) is unprecedented in the PBDs, and may indicate a more reactive imine form. The OBD-5,11-diones of type **14** were also synthesised by reductive cyclisation of the nitro esters (**5**). In contrast to the PBD system, ring closure was rapid (30 min) at room temperature, probably owing to the electron-withdrawing effect of the C-ring oxygen.

[‡] IR (KBr): 1618 (amide), 1712 (ketone), and 3330 cm⁻¹ (amine); ¹H NMR (200 MHz, CD₃SOCD₃): δ 3.69 (octet, *J*₁ 9.2; *J*₂ 7.8; *J*₃ 3.2 Hz, C-11), 4.83 (d, *J* 7.8 Hz, C-11a), oxopropyl methylene 3.07 (dd, *J*₁ 16.9, *J*₂ 3.2 Hz), and 2.62 (dd, *J*₁ 16.9, *J*₂ 9.2 Hz).

In conclusion, we have prepared the oxazolobenzodiazepine ring system (**2**) *via* a novel route and shown that the N(10)-C(11) carbinolamine form appears to be more stable than the related PBD carbinolamines. Unlike the PBD system, the OBD imine form (**12**) undergoes a facile stereospecific reaction with acetone under acid catalysis to afford a C(11)-addition product. The reactivity of the imine form of this system suggests that, like the PBDs, these compounds may have the potential to bind to DNA.

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