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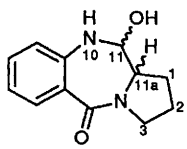
The new carbinolamine-containing oxazolo[2,3-*c*][1,4]benzodiazepine ring system has been synthesized, and its reactivity and stability have been compared with properties of the analogous pyrrolo[2,1-*c*][1,4]benzodiazepine system found in the DNA-binding anthramycin antitumour antibiotics.

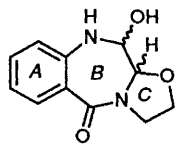
Recently there has been interest in modifying and extending the recognition patterns of DNA-binding ligands towards GC-selectivity,[1] as the 5′-flanks of some oncogenes are GC-rich and many successful anticancer drugs are GC-selective.[2] Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) antitumour antibiotics 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 PBDs[5] 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 (CH_2Cl_2, 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 (^{1}H NMR) and hydrate $CH(OH)_2$ signals were observed by ^{1}H NMR spectroscopy.

Reductive cyclization of aldehydes of type (**6**) under mild conditions (H_2, 10% Pd–C, MeOH, 15 min, room temp., or



(1)



(2)

† Part of this work (M. E. D.) was carried out at the Division of Medicinal Chemistry, College of Pharmacy, University of Texas at Austin, USA.

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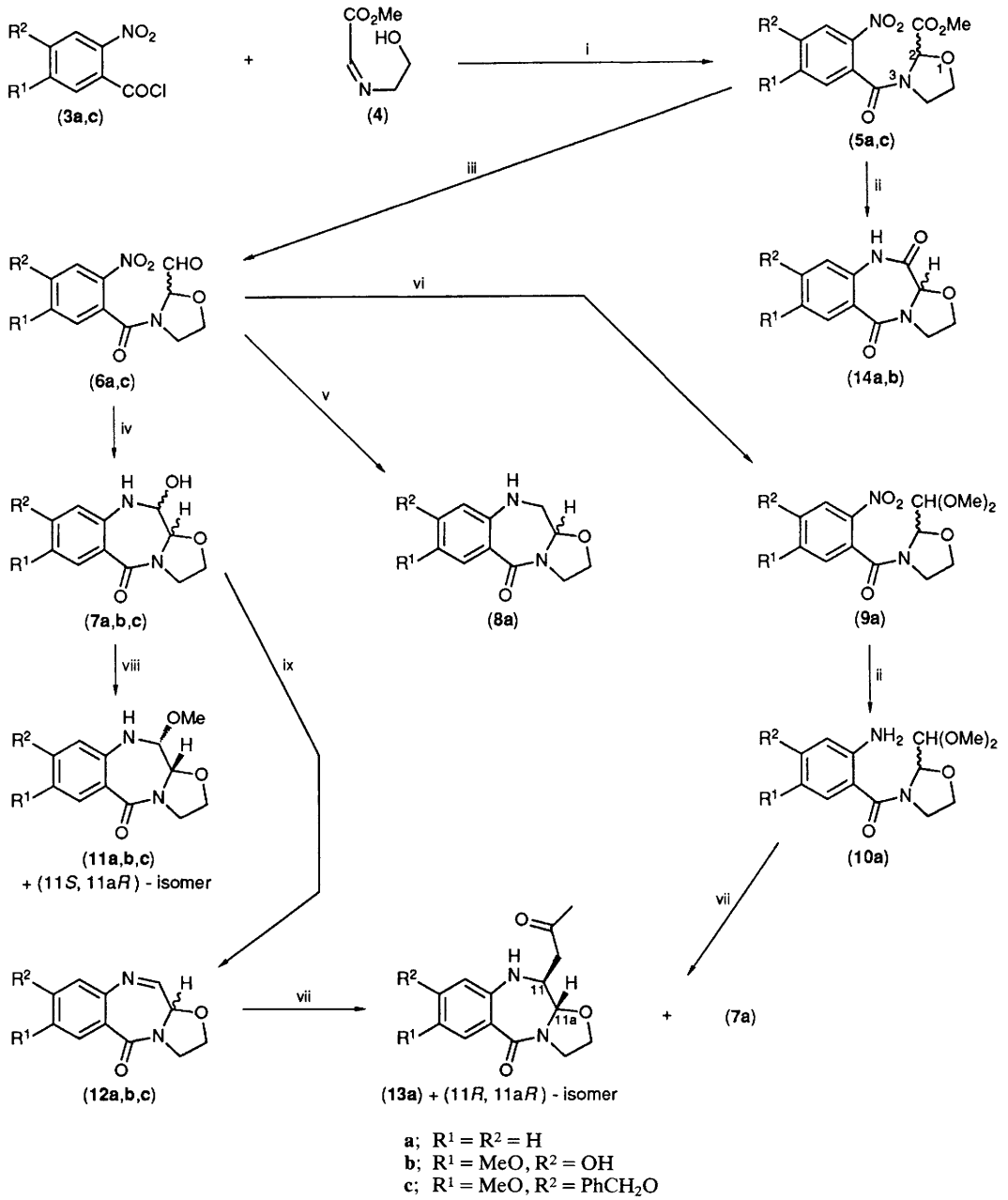

Scheme 1. *Reagents*: i, pyridine, CH_2Cl_2, 0 °C, 20 min; ii, 10% Pd–C, H_2, atm. press., MeOH, 30 min; iii, Bu^i_2AlH, toluene, −78 °C, 30 min; iv, 10% Pd–C, H_2, atm. press., MeOH, 15 min, or $SnCl_2{\cdot}2H_2O$, MeOH, reflux, 90 min; v, 10% Pd–C, H_2, atm. press., MeOH, 72 h; vi, $(MeO)_3CH$, Dowex 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 (11*R*,11a*S*) and (11*S*,11a*R*) 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.

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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, CD_3SOCD_3): 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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References

1 L. H. Hurley, *J. Med. Chem.*, 1989, **32**, 2027.
2 W. B. Mattes, J. A. Hartley, K. W. Kohn, and D. W. Matheson, *Carcinogenesis*, 1988, **9**, 2065.
3 L. H. Hurley, T. Reck, D. E. Thurston, D. R. Langley, K. G. Holden, R. P. Hertzberg, J. R. E. Hoover, G. Gallagher, Jr., L. F. Faucette, S.-M. Mong, and R. K. Johnson, *Chem. Res. Toxicol.*, 1988, **1**, 258.
4 D. E. Thurston, M. E. Davis, and G. B. Jones, *J. Pharm. Pharmacol.*, 1988, **40**, 57P.
5 D. E. Thurston and D. R. Langley, *J. Org. Chem.*, 1986, **51**, 705.

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