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# SYNTHESIS AND STRUCTURE OF ANTHRAMYCIN ANALOGS VIA HYDRIDE REDUCTION OF DILACTAMS

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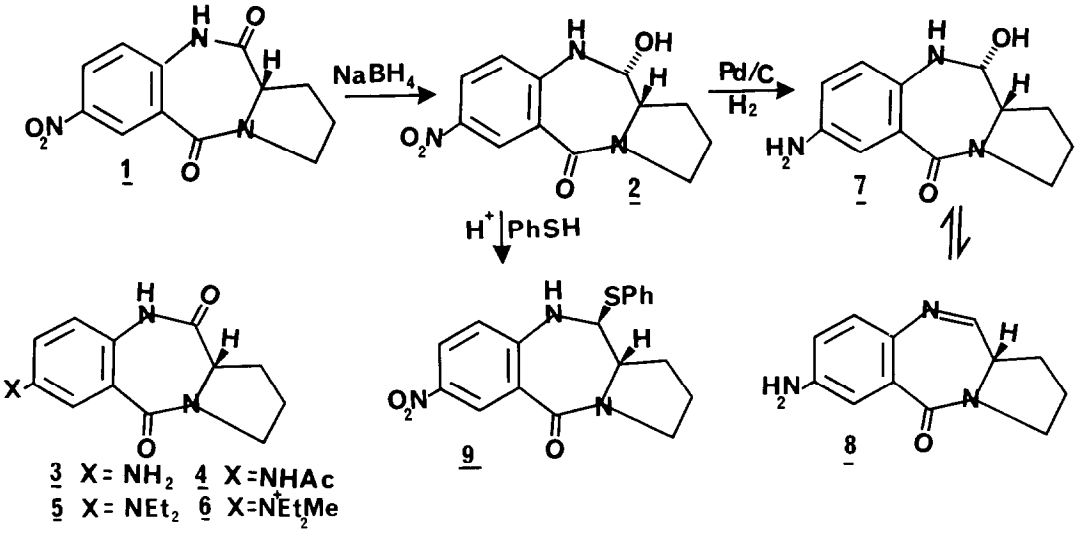
Abstract

Hydride reduction of pyrrolo[1,4]benzodiazepine-5,10-diones to carbinolamines is possible if a sufficiently electron-withdrawing group is present on the aromatic ring; the X-ray structure of one such product is given.

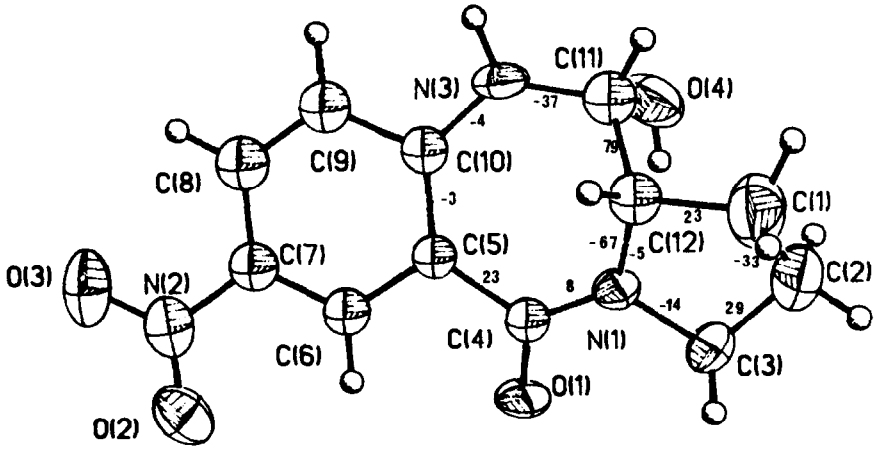
The pyrrolo[1,4]benzodiazepine group of antitumor antibiotics, of which anthramycin is the best-known member, is one of the most interesting classes of DNA-binding drugs. Of all drugs which interact with DNA, the anthramycin group is the only one[1] which unquestionably forms reversible, covalent DNA-drug linkages. Synthetic studies in the anthramycin area have focused on methods to generate the carbinolamine portion since that is the DNA binding site and it is the most sensitive functionality in the molecule. Two routes to these carbinolamines have been published, one involving reductive cyclization of a nitro aldehyde[2] and the other hydride reduction of a pyrrolo[1,4]benzodiazepine-5,10-dione (or a derivative).[3] Recently the limitations of this latter, dilactam, route have been investigated and it has been shown that for most pyrrolo[1,4]benzodiazepine-5,10-diones hydride overreduction to amino alcohols occurs.[4] We have been interested in the dilactam route since (among other reasons) it provides an easy way to produce $^{3}H$ labeled anthramycin analogs for DNA binding studies by using sodium boro[$^{3}H$]hydride. Our results presented herein, along with the recent work of Thurston and co-workers[4] should help to establish the applicability of the dilactam route.

The reaction of 5-nitroisatoic anhydride[5] with L-proline methyl ester in pyridine gave the dilactam *1* in 66% yield.[6,7] A threefold excess of $NaBH_4$ reduced a saturated solution of *1* in MeOH to give the carbinolamine *2*. Addition of water after 10 min precipitated *2* as yellow crystals (68%).[8] At most, trace quantities of overreduction products formed. Replacing the nitro group in *1* with other functional groups on the aromatic ring prevented carbinolamine formation. In the case of the amine *3* (from *1* and 10% Pd/C-$H_2$, MeOH) the system was sufficiently electron-rich so that hydride attack by $NaBH_4$ did not take place.[9] At the other extreme, conversion of *3* to *5* ($NaBH_4$-HOAc) and methylation with $H_3COSO_2F$ gave *6*, which was inert to methanolic $NaBH_4$ due to deprotonation of the amide (as shown by reversible changes in *6*'s UV spectrum, from 242 and 294 to 276 and 325 nm). Compound *4* was slowly reduced by a large excess of $NaBH_4$ to give ring opened, overreduction products, in contrast to *1*. For overreduction to occur, the carbinolamine ring must first dissociate. This can take place either by ejection of the carbinolamine nitrogen as an anion, or the nitrogen can first be protonated, opening to an amino aldehyde. The nitro group prevents this latter process. Our results, along with other recent work,[4] suggest that functional groups which are able to reduce nitrogen basisity, and thus disfavor protonation, allow the synthesis of anthramycin analogs by the hydride reduction of dilactams. While incorporation of the newly-formed carbinolamine nitrogen into a phenyloxazoline ring (as was done in the original anthramycin synthesis[3]) is one way to control nitrogen basisity, the synthesis of *2* shows that other approaches can also succeed.



The substituents on the aromatic ring also affect the stability of the carbinolamine. Compound *7*, unlike *2*, readily dehydrated upon recrystallization from EtOAc to give *8*.

Since only a few crystal structures of molecules in the anthramycin family were available, and none with a free hydroxyl at C11, *2* was subjected to X-ray crystallography.[10] An ORTEP drawing of the result is shown below, including selected torsion angles and bond lengths. The twist of the molecule, $29^0$ (defined as the dihedral angle between the 6 and 5 membered rings), is intermediate between the value in tomaymycin ($9^0$)[11] and anthramycin methyl ether ($45^0$)[12]. The 7 membered ring is a boat with the hydroxyl group almost underneath the 7 membered ring. While an axial oxygen conformation is expected to be most stable in light of the anomeric effect, this effect should be less pronounced in pyrrolo[1,4]benzodiazepines since the lone pair of the nitrogen at N3 may be thought of as part of a vinylogous urea. Taking the difference in bond lengths between the N3–C11 and N1–C12 bonds as a rough measure of the strength of the anomeric effect (N3–C11 is shorter) the difference is only 0.02 Å for *2* (due to the *p*-nitro group), 0.05 Å for anthramycin and 0.07 Å for tomaymycin. It is therefore not surprising that treatment of *2* with PhSH and catalytic $CF_3CO_2H$ gave the equatorial PhS-derivative *9*.[13] Recently other examples of equatorial isomers at C11 in anthramycin analogs have




| | | | |
|---|---|---|---|
| N3–C11 | 1.445(7) Å | N1–C4 | 1.328(6) |
| C11–O4 | 1.420(8) | C4–O1 | 1.243(6) |
| C11–C12 | 1.517(8) | C4–C5 | 1.499(7) |
| C12–N1 | 1.463(7) | C5–C10 | 1.416(7) |
| | | C10–N3 | 1.341(6) |

appeared[4,14] and underscore the fact that the stereochemistry at C11 of the anthramycin-DNA adduct has not yet been experimentally determined.

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6. All new compounds gave confirmatory elemental analyses or in the case of *8* the expected high-resolution parent ion, and spectral data.
7. Compound *1*: mp 253°(ethanol). ir(Nujol) 3260, 1699, 1635. NMR(DMSO) 8.60 (d, J=4.5, 1H) 8.37 (dd, J=4.5, 13, 1H) 7.35 (d, J=13, 1H) 4.2 (m, 1H) 3.5 (m, 2H) 1.7-2.3 (m, 4H).
8. Compound *2*: mp (MeOH) 215°, decomp. ir(Nujol) 3460, 3305, 1610. NMR (DMSO) 8.67 (d, J=2.7, 1H) 8.01 (dd, J=2.7, 9.2, 1H) 6.84 (d, J=9.2, 1H) 4.92 (s, 1H C11), 3.8 (m, 1H) 3.7-3.6 (m, 2H) 1.75-2.3 (m, 4H).
9. For brevity, only the carbonyl ir bands ($cm^{-1}$) and aromatic $^1H$ NMR resonances are given for *3-6*. *3*: mp 233-234, ir ($CHCl_3$) 1680, 1615; nmr 8.00 (s, 1H) 6.80 (s, 2H). *4*: mp 293-294, ir ($CHCl_3$) 1682, 1623; 8.05 (s, 1H) 7.80 (dd, J=8,1, 1H) 7.15 (d, J=8, 1H). *5*: mp 253-255, ir ($CHCl_3$) 1682, 1610; 7.27 (s, 1H), 6.96 (s, 2H). *6*: mp 232-233 (decomp) ir (nujol) 1696, 1629; 8.15 (d, J=2, 1H) 7.96 (dd, J=8,2, 1H) 7.42 (d, J=8, 1H). *8*: nmr 7.61 (d, J=4, 1H), 7.27 (d, J=2.8, 1H) 7.13 (d, 8.5, 1H), 6.84 (dd, J=2.8, 8.5, 1H).
10. Recrystallized from MeOH-EtOAc, a yellow crystal 0.3 x 0.3 x 0.15 mm, was assigned the orthrorhombic space group $P2_12_12_1$ with unit cell parameters a=6.5326(14), b=7.1736(19) c=27.7776(69) A, Z=4. A total of 847 unique reflections were collected with MoK$_\alpha$ radiation on a Nicolet $R3_m1E$ diffractometer at 25°. The structure was solved by the SHELXTL series of programs with anisotropic refinement of all N and O atoms and carbons C1-C3. The final $R_w$ based on $F^2$ was 6.45%. The H atoms on N and O were located in a Fourier difference map and the H on C were inserted in calculated positions and constrained to ride with the heavy atom.
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13. The proton at C11 is at 4.84 with J=11. The other nmr, ir and elemental analysis data are consistent with *9*. The electron impact mass spectrum shows no parent, but a strong M-(PhSH). In *2*, with an axial substituent at C11 and no observed coupling, the dihedral angle between protons C11 and C12 is 74°.
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