Tetrahedron Letters,Vol.25,No.25,pp 2649-2652,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# LIMITATIONS AND FACTORS AFFECTING THE LACTAM REDUCTION APPROACH TO THE SYNTHESIS OF ANTHRAMYCIN ANALOGS

David E. Thurston*, Pravin T.P. Kaumaya, and Laurence H. Hurley
College of Pharmacy, University of Texas at Austin
Austin, Texas 78712

Abstract: The limitations and factors affecting the hydride reduction of pyrrolo[1,4]benzodiazepine-5,10-diones to anthramycin-type analogs have been explored.

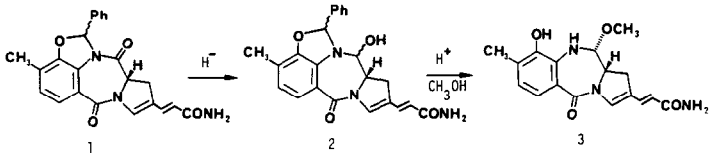
Anthramycin, sibiromycin, tomaymycin and the neothramycins belong to the pyrrolo[1,4]benzodiazepine(P[1,4]B)group of antitumor antibiotics.[1] Previous investigations have provided information on the precise manner in which these drugs bind to DNA[2] and on the probable features responsible for their cardiotoxicity.[3] We have suggested[3] a rational approach to the development of clinically useful drugs in this series, and have embarked[4] upon investigations designed to provide versatile synthetic methodologies which should allow us to test our SAR predictions.[5]

Two synthetically useful methods have been published,[5] that lead to compounds possessing a carbinolamine moiety (or its chemical equivalent) contained within a P[1,4]B ring system. Catalytic reductive cyclization[6] of a nitro aldehyde has provided a total synthesis of tomaymycin and we have also investigated[4,7] the applicability of this approach to other analogs. The second method which is the subject of this paper, involves hydride reduction of a P[1,4]B-5,10-dione (dilactam), a technique utilized[8] by Leimgruber and co-workers for the total synthesis of anthramycin. The results presented here provide insights into the limitations of this approach.

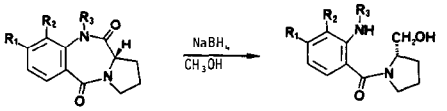
The final step of the synthesis of anthramycin methyl ether (AME)(3) involves reduction of the dilactam (1) with sodium borohydride (SBH) in methanol at 5°C (or lithium aluminium hydride in THF at -60°C) to afford the intermediate carbinolamine (2), which is then treated with methanolic HCl to hydrolyze the phenyloxazoline ring and form the carbinolamine methyl ether (3).

To investigate the generality of this procedure we first prepared[9,10] dilactams 4a and 4b which failed to reduce with SBH under similar conditions. This was attributed to initial reaction of the hydride reducing agent with the amidic N-10 proton (and the C-9 hydroxyl proton in the case of 4b) followed by precipitation of an insoluble complex that is not further reduced.

In order to remove the acidic N-10 proton to facilitate reduction and to observe the effects of increasing steric bulk at the N-10 position, a series of N-substituted dilactams 4c-4h was prepared.[9,10] In each case a mixture of starting material and the corresponding acyclic amino alcohol (5c-5h) resulted from addition of SBH to a methanolic solution of each dilactam at 5°C. These reactions were carefully followed by TLC-MS and although transient fluorescent materials were sometimes observed, carbinolamine species could not be isolated.




1 2 3

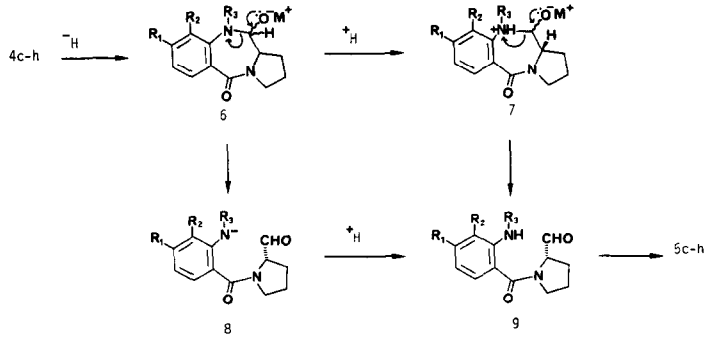



4 5

| 4,5 | $R_1$ | $R_2$ | $R_3$ | 4,5 | $R_1$ | $R_2$ |
|---|---|---|---|---|---|---|
| a | H | H | H | f | H | H |
| b | $CH_3$ | OH | H | g | H | H |
| c | H | H | $CH_3$ | h | H | H |
| d | H | H | $CH_2CH_3$ | i | H | $OCH_3$ |
| e | H | H | $CH_2CH_2CH_3$ | j | $CH_3$ | $OCH_2Ph$ |

It seems likely that overreduction of the dilactam is due to dissociation of the initial carbinolamine complex (6) to the amino aldehyde species (9) which is further reduced to the acyclic amino alcohol (5). Since dissociation of the carbinolamine to the amino aldehyde is the critical step that commits the reaction to proceed to overreduction, we considered factors that may favor this process. First, transient protonation of the nitrogen by methanol may occur, when the nitrogen has sufficient basicity, thus facilitating dissociation to the amino aldehyde (6 → 7 → 9). Secondly, if dissociation results in the negatively charged species 8 then the process 6 → 8 → 9 will be favored if resonance stabilization can occur through the aromatic ring.

Hubert and co-workers have examined[11] an analogous system in which they have reduced para-substituted-N-phenylsuccinimides with SBH in methanol. Based upon the products obtained, and whether the p-substituents are electron withdrawing or donating, these workers favor the stabilization of a charged nitrogen as the most reasonable explanation.

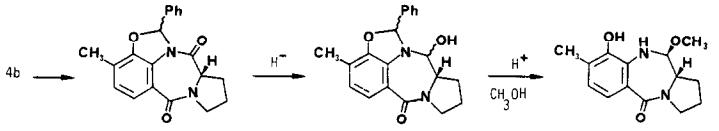



Similarly, according to Gaylord,[12] the prerequisite for hydride overreduction of certain disubstituted amides and some lactams to acyclic alcohols is the presence of strongly electron withdrawing

substituents on the amide nitrogen and Weygand[13] has commented that the aromatic component of N-methylanilides furnishes the required mesomeric resonance to stabilize a nitrogen anion.

In order to investigate whether the "ortho-amidophenyl" N-10 substituents of dilactams 4c-4h allowed extension of resonance from N-10 in a similar manner, the ring substituted dilactams 4i and 4j were prepared, anticipating that the increased electron density of the aromatic rings might prevent stabilization of intermediates of type 8. However, these dilactams failed to reduce under similar conditions. Since steric factors could be excluded, based on the reactivity of 4h, the lack of reactivity was attributed to the ring substituents which tend to maintain electron density on the nitrogen by reducing resonance into the ring. This would facilitate interaction of the nitrogen lone pair with the adjacent carbonyl, hence decreasing its electrophilicity towards approaching hydride ion.

These results suggested that the success[8] of Leimgruber in obtaining the carbinolamine was dependent upon the presence of the phenyloxazoline ring system. We felt that it was important to model this reaction to determine its general applicability to the synthesis of compounds containing a 9-phenolic group. The hydroxy lactam 4b was therefore treated with benzaldehyde dimethyl acetal to afford the phenyloxazoline 10.




10 11 12

Treatment of 10 in methanol with 4.2 equivalents of SBH gave one product quantitatively as visualized by TLC, the reaction usually being complete within 4 hours. The product was isolated by quenching with water and extraction into ethyl acetate which was dried and evaporated to a colorless glue. Trituration with ether afforded a white solid (mp 155-158°C, dec.). This material[10] gave an m/e of 336, corresponding to a mixture of the epimeric carbinolamines (11). Treatment of a methanolic solution of 11 with 0.01 N HCl at room temperature caused immediate reaction as visualized by TLC to afford, after workup, a yellow solid (mp 75-78°C). Mass spectroscopy gave an m/e of 230 and in DMSO-d6, PMR demonstrated the presence of a methoxyl signal at 3.38 ppm, and a non $D_2O$-exchangeable doublet at 4.4 (J=9.45 Hz), thus confirming[14] the structure as the methyl ether 12. It is noteworthy that the determined stereochemistry at C-11, as shown in structure 12 is opposite to that reported for AME,[8] tomaymycin methyl ether[6] and the thioether[5] prepared by Kaneko and co-workers. A detailed discussion of the C-11 stereochemistry of both synthetic and naturally occuring P[1,4]B compounds will form the basis of a future publication.[7]

Our success in obtaining the carbinolamine methyl ether (12) by SBH reduction of 10, provides evidence for the critical role of the phenyloxazoline ring system in limiting the reduction to the carbinolamine stage, which may be rationalized by considering nitrogen protonation rather than the alternative mechanism involving resonance extension from the nitrogen. The inclusion of N-10 into a phenyloxazoline ring, presumably lowers the electron density on the nitrogen (base weakening) via inductive transmission through the benzal carbon (e.g., pkb's: piperidine (2.8[15]) vs. morpholine (5.6[15]) and pyrrolidine (2.7[15]) vs. oxazolidine (5.7[16])) and reduction in the resonance effect of

the C-9 oxygen in 10 vs. 4i. The nitrogen is thus less readily protonated, reducing the possibility of a dissociation mechanism of type 7→9. It is also noteworthy that various 11-oxo-derivatives of P[1,4]B's have been prepared[17-19] but could not be converted to the corresponding carbinolamines by direct reduction with simple hydride reducing agents.

We therefore conclude that SBH reduction of a dilactam is only useful for the preparation of analogs possessing C-9 hydroxyl substituents, formed via hydride reduction of their phenyloxazoline derivatives. Preliminary attempts to use both known and novel techniques for the removal of C-9 hydroxyl, amino or thiol substituents in similar model compounds have not been encouraging due to the sensitivity of the carbinolamine methyl ether.

Acknowledgement. Support for this work was provided through CA-30349 and CA-35318.

References and Footnotes

1. For a review see: Hurley, L.H. J. Antibiotics, 1977, 30, 349. For newer members of this class of compounds see: Kunimoto, S.; Masuda, T.; Kanabayashi, N.; Hamada, M.; Naganawa, H.; Miyamoto, M.; Takeuchi, T.; Umezawa, H. J. Antibiotics, 1980, 32, 665; Shimizu, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Fujimoto, K. J. Antibiotics, 1982, 35, 972.
2. Petrusek, R.L.; Anderson, G.L.; Garner, T.F.; Quinton, F.L.; Fannin, L.; Kaplan, D.J.; Zimmer, S.G.; Hurley, L.H. Biochemistry, 1981, 20, 1111.
3. Thurston, D.E.; Hurley, L.H. Drugs of the Future, Correlates in Pharmacostructures, 1983, 8, 957.
4. Thurston, D.E.; Kaumaya, T.P.; Hurley, L.H. 185th ACS Natl. Mtg. Abstracts, 1983, MEDI 31.
5. Kaneko and co-workers recently reported an alternative approach via the aluminium-amalgam reduction of an imino thioether prepared from the corresponding dilactam. Using this technique, oxotomaymycin was converted to tomaymycin methyl ether in six steps with an overall yield of 29%. the general synthetic utility of this approach is currently under evaluation in our laboratory. Kaneko, T.; Wong, H.; Doyle, T.W. Tet. Letters, 1983, 24, 5165.
6. Tozuka, Z.; Takasugi, H.; Takaya, T. J. Antibiotics, 1983, 36, 276.
7. Thurston, D.E.; Kaumaya, T.P.; Hurley, L.H., manuscript in preparation.
8. Leimgruber, W.; Batcho, A.D.; Czajkowski, R.C. J. Am. Chem. Soc., 1968, 90, 5641.
9. Dilactams 4a-4j were prepared by conventional methods. For example, see Wright, W.B. Jr.; Brabander, H.J.; Greenblatt, E.N.; Day, I.P.; Hardy, R.A., Jr. J. Med. Chem., 1978, 21, 1087 and Reference 8 above. N-Alkyl substituents were added using the method of Johnstone, R.A.W., Rose, M.E. Tetrahedron, 1979, 35, 2169.
10. Satisfactory NMR, CMR, IR and high and low resolution MS data obtained for each novel compound.
11. Hubert, J.C.; Wijnberg, J.B.P.A.; Nico Speckamp, W. Tetrahedron, 1975, 31, 1437.
12. Gaylord, N.G. J. Am. Chem. Soc., 1954, 76, 285.
13. Weygand, F.; Mitgau, R. Chem. Ber., 1955, 88, 301.
14. IR(Nujol)3500-2300,(1725;weak),1605(shoulder at 1615),1555,1195,1075 $cm^{-1}$. NMR(200MHz,DMSO-d6,$\delta$) 1.78-2.40(m),2.18(s),2.96-3.79(m),3.38(s),4.4(d,1H,J=9.45Hz),5.69(bs,1H),6.7(d,1H, J-7.85Hz), 6.95(d,1H,J=7.89Hz), a small amount of the imine form was also present:7.10(d,1H,J=8.41Hz),7.25 (d,1H,J=8.41Hz),7.92(d,1H,J=4.20Hz);$D_2O$ shake caused a loss of the phenolic-OH signal at 5.69. EI mass spectrum 230($M^+$-$CH_3OH$,70),215(10),201(20),185(10),174(12),160(20),149(40). Calcd for $C_{13}H_{14}N_2O_2$-$CH_3OH$=230.1055, observed mass=230.1060.
15. The Merck Index; 10th Edition, Merck and Co., Inc., Rahway, NJ (1983).
16. Predicted from the Taft equation: Perrin, D.D., Dempsey, B., Serjeant, E.P., "pKa Prediction for Organic Acids and Bases", Chapman and Hall, New York (1981), p. 42.
17. Massa, S.; De Martino, G. Il Farmaco-Ed.Sc., 1978, 34, 666.
18. Kariyone, K.; Yazawa, H.; Kohsaka, M. Chem. Pharm. Bull., 1971, 19, 2289.
19. Carey, F.A.; Guiliano, R.M. J. Org. Chem., 1981, 46, 1366.

(Received in USA 6 February 1984)