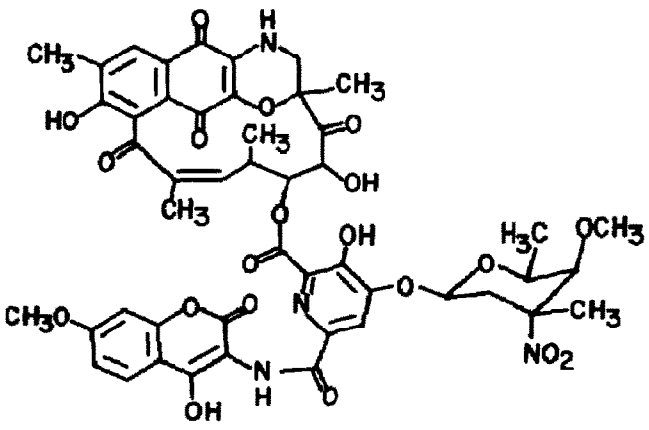
Tetrahedron Letters Vol. 21, pp 3257 - 3260 0040-4039/80/0815-3257$02.00/0

AN APPROACH TO THE CONSTRUCTION OF THE AROMATIC PORTIONS OF NAPHTHOMYCIN AND THE RUBRADIRINS - NUCLEOPHILIC ADDITIONS TO UNSYMMETRICALLY SUBSTITUTED NAPHTHOQUINONES

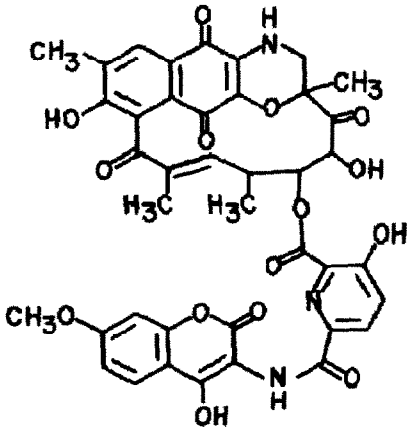
Alan P. Kozikowski* and Kiyoshi Sugiyama
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260
and
James P. Springer
Merck, Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065

Summary: *A Diels-Alder entry into the highly substituted naphthoquinones present in the rubradirins and naphthomycin is described.*

In this letter we present a simple scheme for generating naphthoquinone derivatives related to part structures present in the ansamycin, naphthomycin,[1] and in the newly isolated antibiotic compounds, the rubradirins.[2] These latter substances, which constitute the focal point of our current interests, have been shown to be potent inhibitors of polypeptide biosynthesis in cell-free systems directed with messenger ribonucleic acid.[3]



Rubradirin



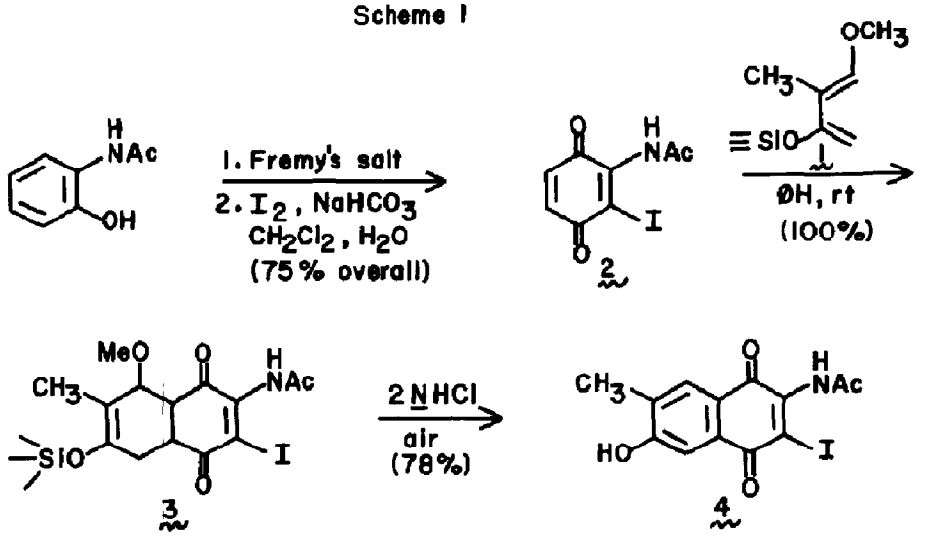
Rubradirin B
(Absolute configuration; 2S, 4S, 5R

We believed at the onset of our investigations that an efficient way to construct such a quinone nucleus was through use of the ubiquitous Diels-Alder reaction. An obvious plan would consist of reacting the known 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (1)[4] with an aminohalo-p-benzoquinone. The halogen substituent of the cycloadduct could, perhaps, at a latter stage be replaced by the required oxygen substituent present in the morpholine ring of the rubradirins.

The reactivity of the known 2-acetamido-3-iodo-p-benzoquinone (2)[5] towards 1 was thus examined first. The preparation of this compound from o-acetamidophenol has been sustantially

improved by carrying out the iodination of the initially formed Fremy's salt product with $I_2/NaHCO_3$ in methylene chloride/water (Scheme 1). This quinone was found to react easily with the diene 1 in benzene at room temperature to afford 3 in quantitative yield after 15h.

Scheme I

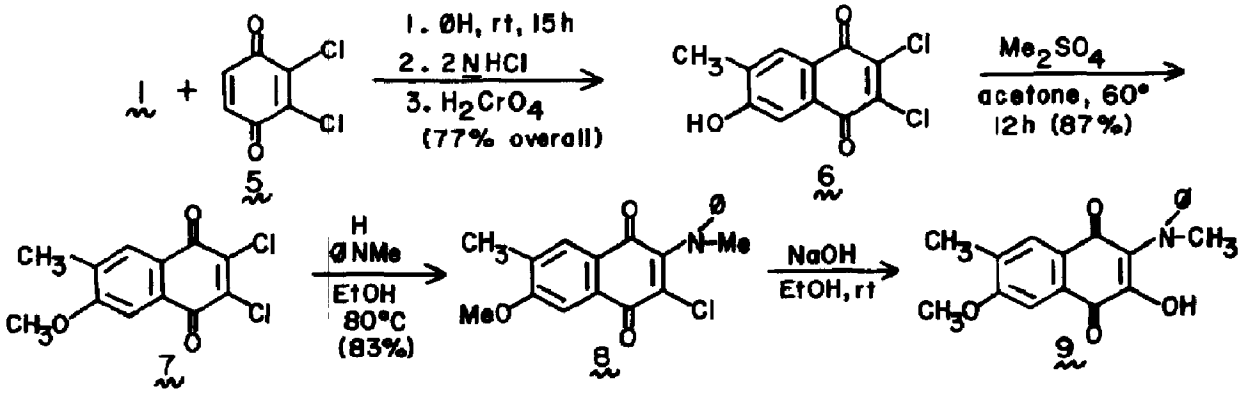


Treatment of the primary cycloadduct with 2 N HCl for 20 min at rt effected unraveling with oxidation (air) to afford the naphthoquinone 4. The regiochemistry of the cycloaddition reaction was judged to be as drawn based on consideration of the electronic and resonance effects of the iodo and acetamido groups.

Attempts to replace the iodo group of 4 by hydroxyl were fraught with difficulty, for the acidic nature of the amide N-H allowed for intervention of an iminoquionone resonance contributor which thus inhibited the desired addition-elimination reaction.[6] When 4 was subjected to more vigorous reaction conditions to effect the desired substitution process, reductive cleavage of th iodo group was found to occur instead.[7]

In pursuit of a more general entry into the desired ring systems, one through which amino groups of varying substitution could be introduced in a separate operation into the quinone nucleus (e.g., a secondary amine which would preclude intervention of the iminoquinone contributor), we chose to vary our scheme by employing 2,3-dichloro-p-benzoquinone[8] as the dienophilic component in the reaction with 1. Again the cycloaddition reaction proceeded smoothly to afford after sequential treatment of the primary cycloadduct with 2 N HCl and chromic acid in acetone/water the 2,3-dichloronapthoquinone 6 in 77% overall yield (Scheme 2).

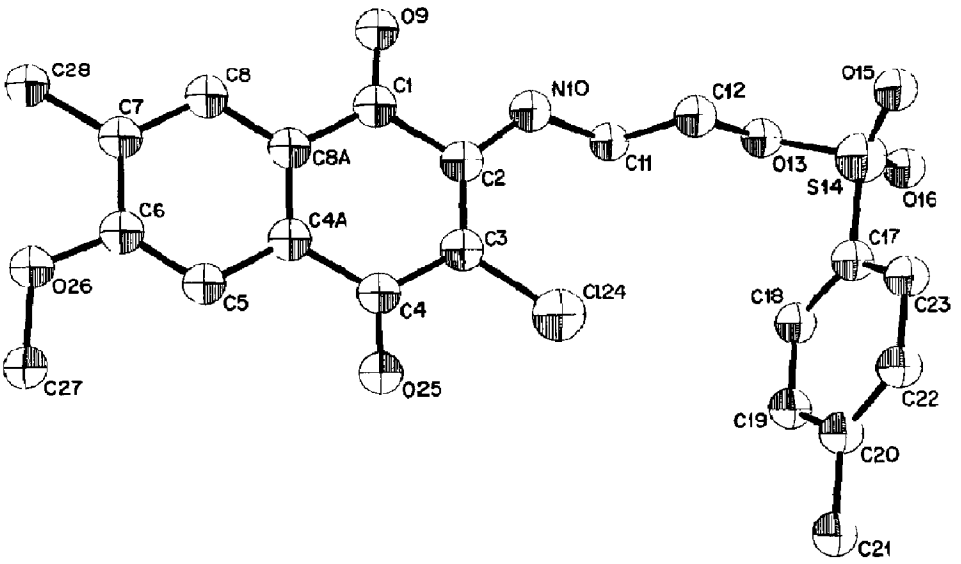
Scheme 2



dimethyl sulfate then afforded 7. In this Diels-Alder reaction, the steric effects of the chlorine substituents outweigh their electronic effects, thus guiding the cycloaddition to the unsubstituted quinone double bond. [9]

The important question we now wished to address was the regiochemistry of nucleophilic addition reactions to this substance. Was the methoxy substituent in the aromatic ring of compound 7 really going to provide sufficient resonance interaction with the quinone carbonyl at C-1 to control the course of addition?[10,11] Reaction of 7 with N-methylaniline did in fact yield a single new compound. This compound on reaction with hydroxide yielded in turn a second new product of addition-elimination (7 → 9, Scheme 2).

In order to confirm that the regiochemistry of the first substitution reaction with 7 was as shown in Scheme 2, we added aminoethanol to this dichloronapthoquinone and then converted this intermediate to a well defined crystalline derivative by preparing its corresponding O-tosylate 10.[12] X-ray analysis substantiated the structural assignment we had made on the basis of resonance considerations.[13]



A computer generated drawing of 10

The work reported herein constitutes one of the very few definitive demonstrations of the ability of a C-6 substituent to control the regiochemistry of nucleophilic addition-elimination reactions through many bonds. Further studies aimed at the development of a general 1,4-oxazine synthesis for the elaboration of materials related to 9 and 10 to the ansa-like moiety of the rubradirins are underway.

Acknowledgement: We are grateful to the Sloan Foundation and to Merck, Sharp & Dohme for financial support.

References and Notes

1. T. H. Williams, J. Antibiotics, 28, 85 (1975).

2. (a) H. Hoeksema, L. Lewis, S. A. Mizsak, J. A. Shiley, D. R. Wait, H. A. Whaley and G. E. Zurenko, J. Antibiotics, 31, 945 (1978); (b) B. K. Bhuyan, S. P. Owen and A. Dietz, Antimicr. Agents and Chemoth., 1964, 91 (1965); (c) C. E. Meyer, ibid., 97 (1965); (d) H. Hoeksema, C. Chidester, S. A. Mizsak and L. Baczynskyj, J. Antibiotics, 31, 1067 (1978); (e) H. Hoeksema, S. A. Mizsak, and L. Baczynskyj, ibid., 32, 773 (1979); (f) S. A. Mizsak, H. Hoeksema and L. M. Pschigoda, ibid., 32, 772 (1979).

3. F. Reusser, Biochemistry, 12, 1136 (1973).

4. S. Danishefsky, C-F. Yan, R. K. Singh, and R. B. Gammill, J. Am. Chem. Soc., 101, 7001 (1979)

5. H. Wunderer, Chem. Ber., 105, 3479 (1972).

6. For a related observation, see I. F. Vladimirtsev, I. Ya. Postovsky and L. F. Trefilova, J. Gen. Chem., 183 (1953).

7. For a related finding, see J. A. Van Allan and G. A. Reynolds, J. Org. Chem., 28, 1019 (1963)

8. J. B. Conant and L. F. Fieser, J. Am. Chem. Soc., 45, 2194 (1921); P. Svec, R. Seifert, and M. Zbirovsky, J. Chromatog., 53, 587 (1970).

9. M. F. Ansell, B. W. Nash and D. A. Wilson, J. Chem. Soc., 3012 (1963).

10. For a review of the addition and substitution chemistry of quinones, see K. T. Finley in S. Patai, Ed., "The Chemistry of the Quinonoid Compounds", Wiley, New York, 1974, Part 2, Chapter 17.

11. FMO theory has been found to be in accord with resonance theory arguments for explaining the regioselectivity of nucleophilic additions. We thank Professor Houk for providing us with a preprint of these findings.

12. 10 ($C_{21}H_{20}ClNO_6S$) crystallized from ethyl acetate as red laths of symmetry $P2_1/c$ with a=17.540(4)Å, b=8.444(3), c=15.313(3) and β=115.49(2)° for a calculated density of 1.46 g/cm^3. Of the 2760 unique reflections measured using CuKα radiation, 1771 (64%) were observed ($I \geq 3\sigma I$). The structure was solved using direct methods and refined using full-matrix least squares techniques. The function $\Sigma w (|F_o| - |F_c|)^2$ with $w = (1/\sigma F_o)^2$ was minimized to give a final unweighted crystallographic R factor of .067. All intramolecular distances and angles are normal and no abnormally short intermolecular contacts were found.[14]

13. Tables of fractional coordinates, temperature factors and bond distances and bond angles for 10 are available from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 IEW.

14. The following library of crystallographic programs was used: "MULTAN 78, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data", University of York, England (1978); "The X-Ray System, Version of June, 1972", TR-192, Computer Science Center, University of Maryland, College Park, Maryland (1972); "ORTEP-II: A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustrations", U. S. Atomic Energy Commission, Report ORNL-3794 (2nd Rev., with Supplemental Instructions), Oak Ridge National Laboratory, Oak Ridge, Tennessee (1970).

(Received in USA 25 April 1980)