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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF THE RUBRADIRIN ANTIBIOTICS. 3. DIELS-ALDER REACTIONS OF UNSYMMETRICALLY SUBSTITUTED QUINONES - A CONFIRMATION OF STRUCTURE.

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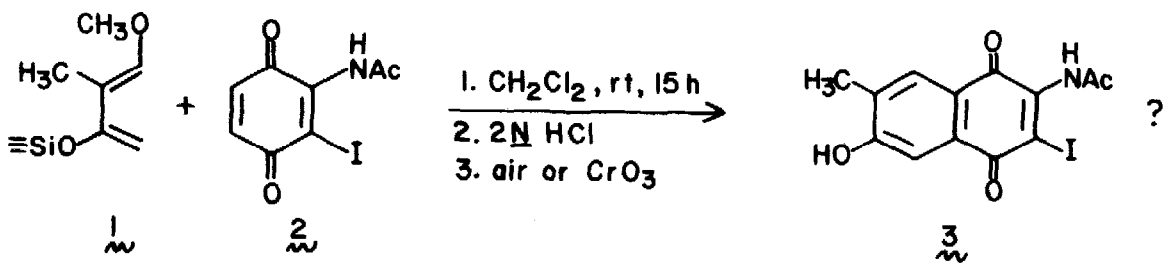
Summary: *The regiochemical course of the Diels-Alder reaction of 2-acetamido-3-iodo-p-benzoquinone with 1-methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene has been unambiguously established through a correlation study.*

In an earlier publication concerning a potential approach to the aromatic portion of the rubradirin antibiotics, we had suggested that the Diels-Alder reaction of 2-acetamido-3-iodo-p-benzoquinone with 1-methoxy-2-methyl-3-trimethylsilyloxybutadiene afforded the napthoquinone 3 after treatment of the initial cycloadduct with 2N HCl and air oxidation (Scheme I).[2] The regiochemistry of this [4+2] cycloaddition reaction was anticipated to be as pictured on the basis of the relative inductive and mesomeric effects of the iodo and acetamido groups. This

Scheme I



1 2 3

notion is supported by the relative size of the σ constants for these two groups. [σ_p (CH_3CONH-) = -0.015; σ_p (I-) = +0.276].[3]

We would now like to describe some additional experiments which verify this original assumption. We believe that these results should be of general relevance to the preparation of part structures exhibited by various ansamycin-related natural products.[4]

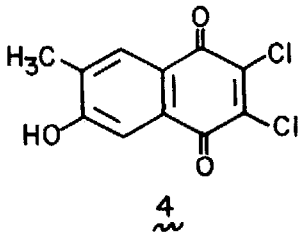
We had reported previously that the 2,3-dichloronaphthoquinone 4 undergoes nucleophilic attack predominantly at C-2, a result confirmed fully by X-ray structural analysis.[2] In order to correlate this result with the above Diels-Alder reaction, we needed merely to carry out an addition-elimination reaction on 4 with ammonia, O-methylate, N-acetylate, and then reductively remove the chlorine atom. Reductive removal of iodine from 3 and O-methylation would provide the appropriate materials for comparison.

The naphthoquinone 4 was thus treated with ammonium hydroxide in ethanol at 75°C for two hours and the product O-methylated with dimethyl sulfate/potassium carbonate in acetone. The intermediate aminonapthoquinone was admixed with acetic anhydride and one drop of sulfuric acid and stirred at 0°C for fifteen minutes to effect N-acetylation. Reductive removal of the chlorine atom was accomplished in turn by subjecting a methanol solution of the acetamidoquinone, 10% Pd/C, and four equivalents of triethylamine to a balloon-filled atmosphere of hydrogen. The acetamidonaphthoquinone 5 was purified by chromatography on silica gel with 40% ethyl acetate-hexanes as eluent in order to separate it from a small amount of the corresponding regioisomer (ratio = 6:1; overall yield 83%). (Scheme II).

The Diels-Alder cycloadduct 3 was next hydrogenated in methanol containing triethylamine over 10% Pd/C to effect removal of the halogen atom (alternatively, the reduction could also be brought about by simply refluxing 3 with two equivalents of triethylamine in xylene). Methylation of the phenolic hydroxyl group with dimethyl sulfate/potassium carbonate in acetone gave 6. (Scheme III). A 300 MHz ^1H NMR of this material revealed the presence of a small amount of a second isomer (ratio = 12:1; 87%).

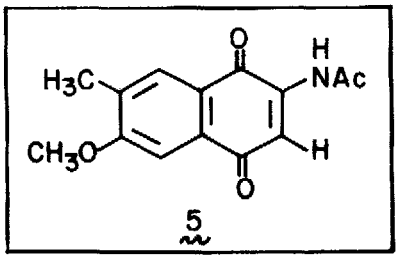
Comparison of the two major isomers generated by these independent routes was made by 300 MHz ^1H NMR analysis. The compounds were in fact found to be *identical*, thus substantiating our original notions regarding the relative directing effects of the heteroatom substituents. 5, 6: m.p. 267-268.5°C (decomp.); 300 MHz ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.86 (s, 1H), 7.74 (s, 1H), 7.46 (s, 1H), 3.99 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H).

Scheme II



4

1. NH_4OH, EtOH
2. Me_2SO_4, K_2CO_3
3. Ac_2O, H^+
4. H_2, 10% Pd/C, Et_3N, MeOH

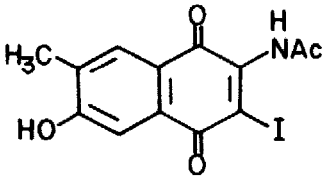


5

+ isomer (6:1)

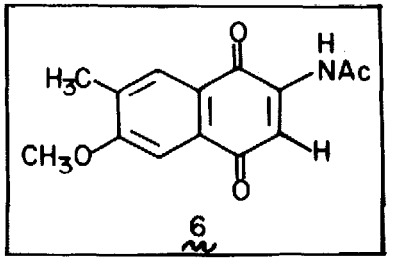
III

Scheme III



3

1. H_2, 10% Pd/C, Et_3N, MeOH
2. Me_2SO_4/K_2CO_3

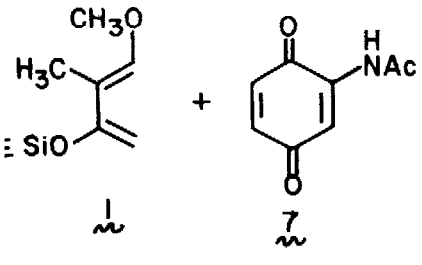


6

+ isomer (12:1)

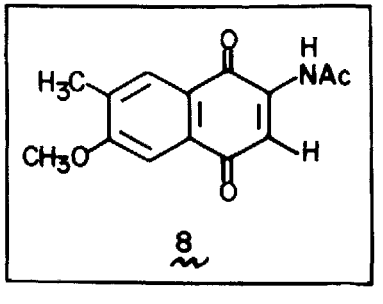
III

Scheme IV



1 + 7

1. CH_2Cl_2, rt
2. 2N HCl
3. CrO_3
4. Me_2SO_4/K_2CO_3



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With this information in hand, it was also of interest to determine whether the acetamido group could alone control the course of the Diels-Alder reaction with 1. The known quinone 7[5] was thus reacted with 1 at room temperature in methylene chloride for fifteen hours. Processing the crude cycloadduct consecutively with 2 N HCl, chromium trioxide, and dimethyl sulfate/potassium carbonate gave a single naphthoquinone 8 (89%). By 300 MHz ^{1}H NMR analysis, this material consisted of a single regioisomer which was identical to that produced by the two routes described above. Thus, *the acetamido group, which is only very weakly electron releasing, is quite capable of steering the Diels-Alder reaction with high selectivity.*[6]

In summary, the results reported herein provide valuable regiochemical information on the use of differentially substituted quinones in the Diels-Alder reaction. Further applications of these findings to the synthesis of the rubradirins will be reported in due course.

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References

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6. All new compounds exhibited satisfactory spectroscopic data (IR, NMR and MS).

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