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# Naphthacenequinones

Joseph J. Hlavka, Panayota Bitha and James H. Boothe

Organic Chemical Research Section
Lederle Laboratories Division of American Cyanamid Company
Pearl River, New York

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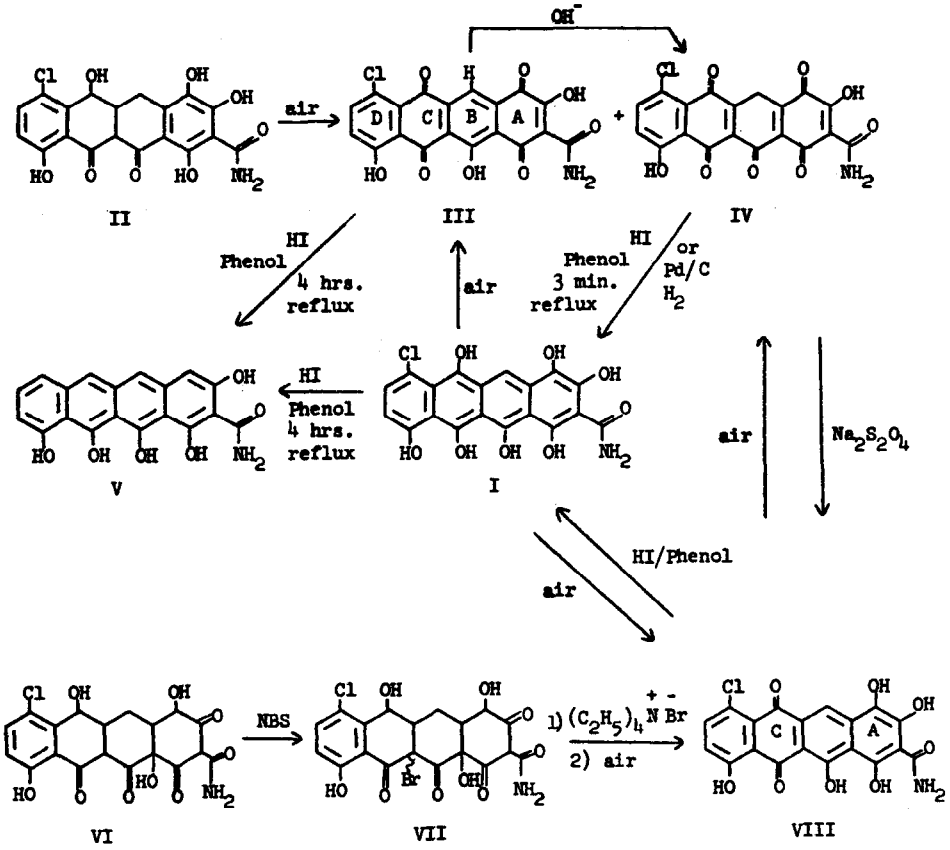
Our recent investigation[1] in the field of substituted pretetramids[2] has been extended to include the oxidation products, i.e. naphthacenequinones, of these and related compounds.

We have found that air oxidation[3] of 4,6-dihydroxy-7-chloropretetramid[4] (I) affords both the diquinone III and, as a minor product, the monoquinone VIII.[5] The diquinone assignment to III was based on composition,[6] spectral properties,[7] and polargraphic analysis. The half wave potential[8] of this material agreed within experimental error with reference quinones. The particular tautomeric form was assigned on the basis of the n.m.r. spectrum[9] which exhibited three aromatic protons, a typical AB splitting pattern due to the two vicinal aromatic protons in the D ring and a singlet due to the proton in the B ring.

A similar oxidation[3] of 7-chloro-4a,12a-anhydro-4-dedimethylamino-4-hydroxytetracycline[1] (II) yielded both III and the tautomeric quinone IV. The tautomeric relationship of III and IV was established by rapid base catalyzed conversion of III to IV. The naphthacene framework of the two quinones (III and IV) was corroborated by both the reduction[10] of IV to 4,6-dihydroxy-7-chloropretetramid, I, (and subsequently to pretetramid V)[11] or by direct reduction[12] of III to the parent pretetramid V.[11] As in the case of III, the diquinoid feature of IV was confirmed *via* polargraphic and spectral analysis.[13]

Further confirmation of structure IV was obtained by a synthetic route. Reaction of 7-chloro-4-dedimethylamino-6-demethyl-4-hydroxytetracycline[14] (VI) with N-bromosuccinimide yielded the 11a-bromo derivative VII. Dehydrohalogenation of VII with tetraethylammonium bromide[15] followed by air oxidation gave the monoquinone VIII.[5] This material, VIII, could be converted to I by a mild reduction step, thus verifying the 1,3,4-trioxy arrangement in ring A. Air oxidation of VIII afforded the diquinone IV which could be reversibly reduced back to VIII with sodium hydrosulfite.

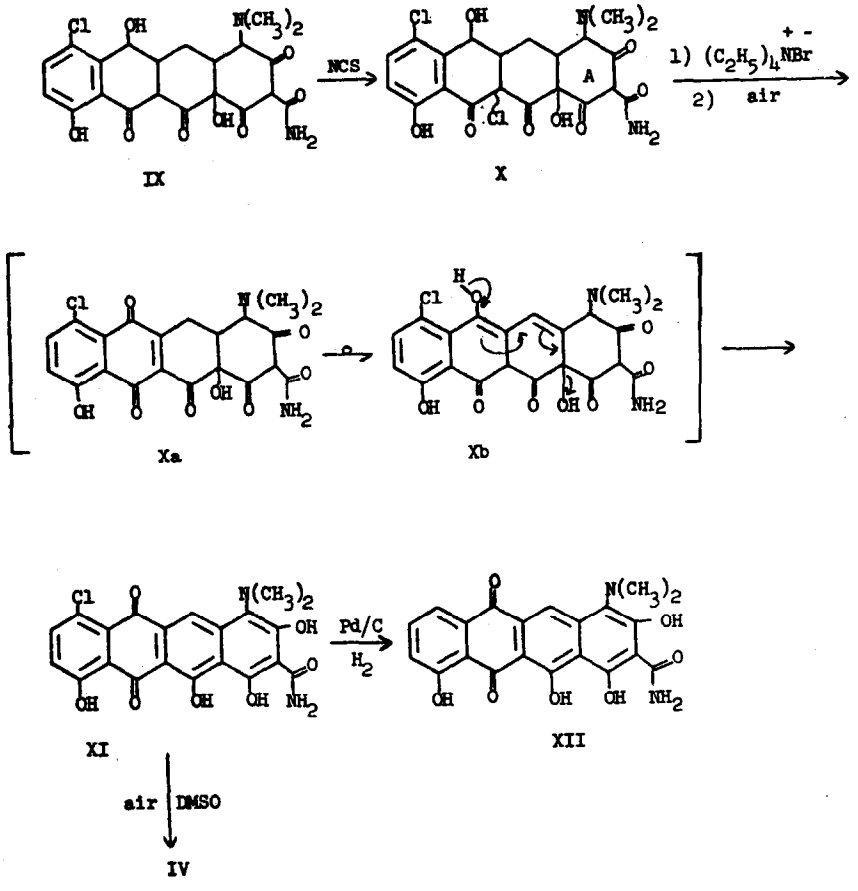
Chart I



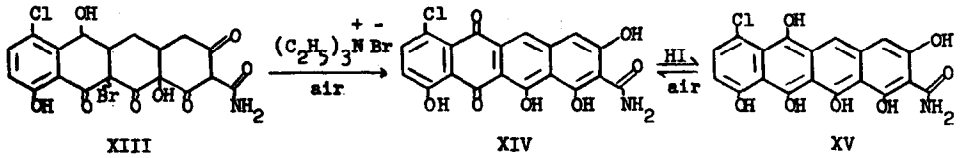

Additional work showed the general nature of the reaction (VII→VIII) by which dehydrohalogenation[16] coupled with air oxidation of an 11a-halo-6,12a-dihydroxy compound, i.e. VII, X, or XIII, occurs with a concomitant elimination of the 12a hydroxyl group to give directly the aromatic A ring and quinoid C ring. Reaction of 7-chloro-6-demethyltetracycline(IX) with N-chlorosuccinimide afforded the 7,11a-dichloro derivative X which on treatment with tetraethylammonium bromide[15] yielded directly 7-chlorotetramid blue[17] (XI) which could be dehalogenated to the known tetramid blue[5] (XII). Air oxidation of XI afforded the diquinone IV. We suggest that this reaction X→XI, proceeds via a normal dehydrohalogenation with tetraethylammonium bromide[15,16] followed by oxidation to the quinone Xa with subsequent tautomerization to Xb. This intermediate Xb can then eliminate water to yield the aromatic A ring

compound XI. An analogous reaction with the 7-dechloro derivative of IX yielded tetramid blue[5] (XII) directly.

Chart II




Similarly the reaction sequence was carried out on the 4-dedimethylamino derivative XIII to yield quinone XIV. Reduction of XIV afforded the substituted pretetramid XV[18] which could be oxidized back to XIV.



## Acknowledgements

We are grateful to Mr. L. Brancone and his staff for the analytical data and to Mr. W. Fulmor and co-workers for the n.m.r. spectra. We wish to express our thanks to Dr. A. Kende and Dr. J. McCormick for their stimulating discussions. Finally, we wish to thank Dr. M. Halwer and his staff for the polarographic analysis.

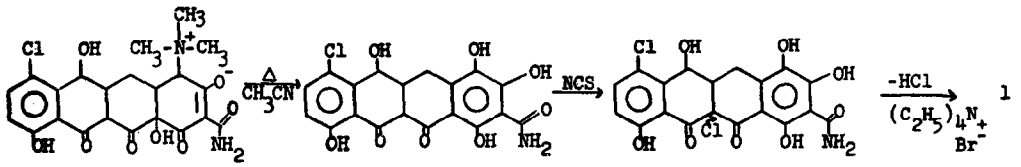
## References

1. J. J. Hlavka, P. Bitha, J. H. Boothe, J. Am. Chem. Soc., 87, 1795 (1965).

2. The name "pretetramid" has been suggested for 1, 3, 10, 11, 12-pentahydroxynaphthacene-2-carboxamide: J. R. McCormick, S. Johnson, and N. Sjolander, J. Am. Chem. Soc., 85, 1694 (1963).

3. Air was bubbled through a dimethyl sulfoxide solution of the pretetramid for twenty-four hours.

4. This material was prepared via the following reaction sequence:




5. a) J. R. D. McCormick, Biogenesis of Antibiotic Substances, Z. Vanek and Z. Hostalek, editor, Academic Press, New York, 1965, p. 73. b) J. R. McCormick and W. Gardner, U.S. Patent #3,074,975.

6. All materials gave acceptable elemental analyses.

7. All ultraviolet curves were taken in concentrated sulfuric acid + 1% sodium borate. The $\lambda_{max}$ for I is 298, 560 and 598 mμ (log ε 4.55, 4.21 and 4.46).

8. The half wave potentials of this material occurred at -0.75 volts and -1.15 volts (versus a calomel electrode) at 25° using 0.1 M magnesium acetate in dimethyl formamide as the solvent.

9. All n.m.r. spectra were measured in deuterated dimethyl sulfoxide with tetramethylsilane as the internal standard using a Varian Model A60 spectrometer.

10. This reduction was effected either by a short reflux (3 minutes) in a hydrogen iodide-phenol solution or catalytically with hydrogen and palladium on carbon.

11. J. McCormick, S. Johnson and N. Sjolander, J. Am. Chem. Soc., 85, 1694 (1963).

12. This reduction was effected by refluxing for four hours in hydrogen iodide-phenol solution.

13. $\lambda_{max}$ 272, 300 and 575 mμ (log ε 4.26, 3.84 and 3.68). We were unable to obtain an n.m.r. spectrum of this material due to its insolubility in most solvents.

14. We wish to thank Dr. R. Esse of the Chemical Process Improvement Department for a sample of this material. He obtained this compound by reducing 7-chloro-4-hydroxytetracycloxide [R. Esse, J. Lowery, C. Tamorria and G. Sieger, J. Am. Chem. Soc., 86, 3874 (1964)] with sodium borohydride.

15. J. R. D. McCormick, R. Winterbottom and P. Bitha, U.S. Patent #3,226,435, December 28, 1965.

16. Earlier work (see above reference) described the dehalogenation of 11a-chloro-6-disubstituted compound to obtain a stable 5a,11a dehydro product.

17. $\lambda_{max}$ 293, 545 and 580 mμ (log ε 4.65, 4.21 and 4.26).

18. Longer heating with hydrogen iodide in phenol yielded pretetramid (see reference 10).