Tetrahedron Letters No.59, pp. 5127-5128, 1970. Pergamon Press. Printed in Great Britain.

SYNTHETIC APPROACH TOWARDS TETRODOTOXIN. I.
DIELS-ALDER REACTION OF α-OXIMINOETHYLBENZOQUINONES WITH BUTADIENE

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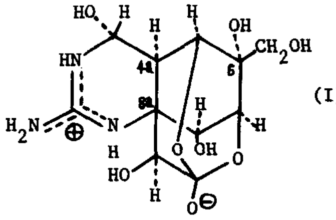
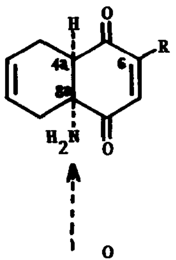
(Received in UK 23 October 1970; received in UK for publication 18 November 1970)

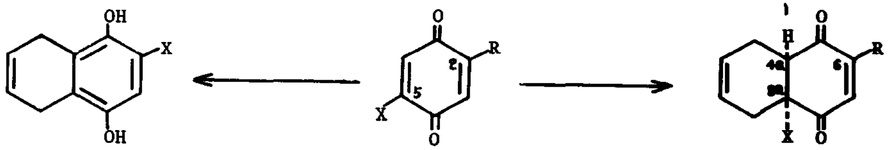
In a synthetic approach towards tetrodotoxin (I)[1], poisonous principle of Japanese puffer fish, our basic plan is to prepare a Diels-Alder adduct (III) from p-benzoquinones (II) having a substituent X, such as a ketone or a carboxylic acid equivalent, and then to introduce an amino group into C-8a by Beckmann or Hofmann type rearrangement on the substituent X. By this plan, it can be possible to introduce the required functional groups at C-4a and C-8a under a control of stereochemistry.

We have chosen α-oximinoethylbenzoquinones as the dienophile (II) from the following reasons: i), acetylhydroquinones, especially 5-acetyltoluhydroquinone, are readily accessible compounds; ii), when a Diels-Alder adduct (III) is obtained, it is ready for the next crucial Beckmann rearrangement without further modifications on the substituent X.



(I) TETRODOTOXIN





(II) (III)

(IV) $X = \underset{CH_3}{C}{=}N{-}OH$

(IIa) R= H, $X = \underset{CH_3}{C}{=}N{-}OH$

(IIb) R= CH_3, $X = \underset{CH_3}{C}{=}N{-}OH$

(IIIa) R= H, $X = \underset{CH_3}{C}{=}N{-}OH$

(IIIb) R= CH_3, $X = \underset{CH_3}{C}{=}N{-}OH$

Diels-Alder reaction using a compound having an α-oximinoalkyl group as a dienophile has not been known as far as we know. Although an oximino group can play as either an electron withdrawing or an electron donating group, it is theoretically possible to cut off or to reduce the electron donating ability under a special condition, such as acidic.

With such a consideration, we first studied the Diels-Alder reaction between α-oximinoethylbenzoquinone (IIa)[2,3] and butadiene. When IIa was heated with the diene in acetonitrile or in ethanol, an adduct (IV)[4] was produced as a major product.[5] On the other hand, when the reaction was carried out in the presence of stannic chloride in acetonitrile at room temperature, another adduct (IIIa)[6] was isolated as a single product.

As the benzoquinone part (II) must have additional one carbon atom at C-2 for our special interest of synthesizing tetrodotoxin (I), the Diels-Alder reaction of 5-(α-oximinoethyl)toluquinone (IIb)[7] and butadiene was studied next. When IIb was heated with the diene in acetonitrile or in ethanol, addition of the diene to IIb occured exclusively in a fassion different from that in the case of IIa; the adduct IIIb[8] was isolated by a chromatography on silica gel in about 30 % yield.[9] For the practical point of view, it is important that the reaction is accelerated by the addition of stannic chloride or cupric fluoroborate. The best condition for the preparation of IIIb was the one in acetonitrile at room temperature in the presence of stannic chloride and the yield of the highly pure, crystalline product was 83 %.

In conclusion, under neutral conditions a delicate balance of electronic (electron withdrawing and donating) and steric factors[10] determines which of the two ethylene linkages of the quinones is preferentially attacked by the diene in Diels-Alder reaction of IIa and IIb. In this connection, it became possible to control the direction of addition of the diene to IIa by selecting a condition. In the presence of a Lewis acid, the ethylene linkage with the α-oximinoalkyl group is preferentially attacked by the diene, because electron withdrawing ability of the substituent is enhanced.

Acknowledgement: Two (Y.K. and T.G.) of us thank the Naito Kinen Zaidan for financial support.

REFERENCES AND FOOTNOTES

1. For the structure elucidation of tetrodotoxin, see: T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, Tetrahedron, 21, 2059 (1965). Other references are cited in this paper.
2. Satisfactory analytical and spectroscopic data were obtained for all the new compounds.
3. IIa was prepared as follows: acetylhydroquinone was converted to oxime (mp 151-3°), which was oxidized to IIa by silver oxide in anhydrous ether (87 % yield)(mp 121-3°dec.).
4. mp 160-3°dec.; ms 219(M$^+$); λ(MeOH) 219 and 280nm (ε 12,100 and 4,300); δ(ppm:DMSO-d_6) 1.95 (3H,s), 5.67(2H), 6.63(1H,s)
5. Less than 5 % of the adduct IIIa was isolated by a chromatography on silica gel.
6. mp 114-6°; ms 219(M$^+$); λ(MeOH) 223nm (ε 8,600); ν(KBr) 1682 cm^{-1}; δ(ppm:DMSO-d_6) 1.80(3H,s), 3.45(1H,dd,J=10,7), 5.70(2H), 6.56(2H,s)
7. IIb was prepared as follows: 5-acetyltoluhydroquinone [E. Kurosawa, Bull. Chem. Soc. Japan, 34, 300(1961)] was converted to oxime (92 % yield)(mp 146-8°), which was oxidized to IIb by silver oxide in anhydrous ether (86 % yield)(mp 133-6°dec.).
8. mp 157-9°; ms 233(M$^+$); λ(MeOH) 238nm (ε 14,200); ν(KBr) 1691, 1663, 1620 cm^{-1}; δ(ppm:CDCl$_3$) 1.79(3H,s), 1.97(3H,d,J=1.2), 3.47(1H,t,J=7.5), 5.73(2H), 6.46(1H,q,J=1.2)
9. 5-Acetyltoluhydroquinone is a by-product of this reaction.
10. Ansell et al. [J. Chem. Soc., 3012(1963)] discussed the factors which of the two ethylene linkages of a quinone is preferentially attacked by a diene.