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SYNTHETIC APPROACH TOWARDS TETRODOTOXIN. II. A STEREOSPECIFIC SYNTHESIS OF A COMPOUND HAVING THE SAME SIX CHIRAL CENTERS ON THE CYCLOHEXANE RING AS THOSE OF TETRODOTOXIN

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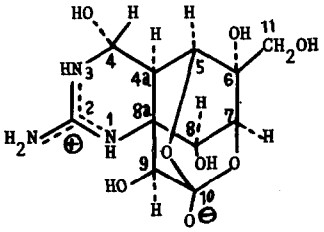
In the preceding paper[1] we have reported a practical preparation of the Diels-Alder adduct II from 5-(α-oximinoethyl)toluquinone and butadiene. We would like to communicate a derivation of II into XIX, which has the same six chiral centers on the cyclohexane ring as tetrodotoxin (I) has.

Beckmann rearrangement of the mesylate III[2,3] in boiling water afforded crystalline amide IV[4] in 61 % yield. Sodium borohydride reduction of IV in methanol at 0° yielded the alcohol V[5] in 96 % yield. Two remarks are made on this reduction: i), as the reagent can approach to the carbonyl group only from the outer side of the cage-like molecule, a highly stereospecific reduction was performed; and ii), only one of the two carbonyl groups is attacked by the reagent. This is understood by the consideration that the preferred conformation of the acetamido group in IV is axial with respect to the cyclohexenedione ring and hence the carbonyl group adjacent to the acetamido group can not be attacked by the reagent.

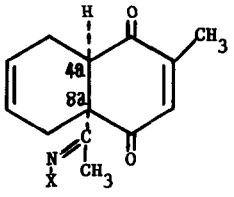
With m-chloroperbenzoic acid in the presence of camphorsulfonic acid, the alcohol V was transformed into the ester VI[6] in 75 % yield. The structure of VI was established mainly from the analysis of nmr spectra of the acetate VII[7] and the ketone VIII[8] derived from VI by a spin decoupling technique. As the formation of the ether linkage is only possible in the compound having configurations shown in the formula VI (except C-10)[9], the configurations of the three chiral centers (C-4a, C-5, and C-8a) were completely established.

Epoxidation of the enone VI with alkaline hydrogen peroxide afforded cleanly a single keto epoxide (IX)[10] in 90 % yield. It is axiomatic that the configurations of newly produced chiral centers must be as shown in the formula IX from the reason that the approach of hydrogen peroxide anion to the enone is possible only from the outer side of the cage-like molecule. With sodium borohydride in methanol at 0° the ketone IX was smoothly reduced to the alcohol X, which was isolated as the acetate XI[11] in 77 % yield from IX. The configuration of the new chiral center (C-8) was assigned from the coupling constant ($J_{7,8}$=0, $J_{5,7}$=1.2) of the nmr spectrum. More convincing evidence about the configuration was obtained from the following experiments.

The alcohol V was converted to the bromide XII with bromine in methylene chloride or with NBS in methylene chloride/t-butanol. Sodium borohydride reduction of the keto epoxide XIII, obtained from XII by alkaline hydrogen peroxide, gave exclusively an alcohol epoxide (XIV), which



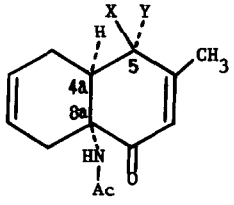
(I) TETRODOTOXIN



(II) X=OH

(mp 157-9°)

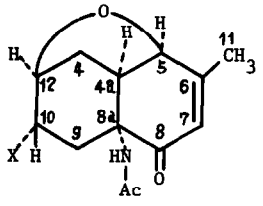
(III) X=OSO_2CH_3
(mp 138-140°)



(IV) X, Y=O

(mp 158-160°)

(V) X=OH, Y=H
(mp 179-181°)

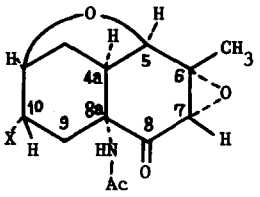


(VI) X=OH (mp 209-211°)

(VII) X=OAc (mp 188-190°)

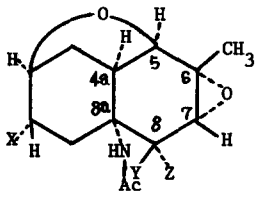
(VIII) ketone at C-10 (mp 124-5°)

(XII) X=Br (mp 181-2°dec.)



(IX) X=OH
(mp 251-2°)

(XIII) X=Br
(mp 201-2°dec.)



(X) X=Y=OH, Z=H

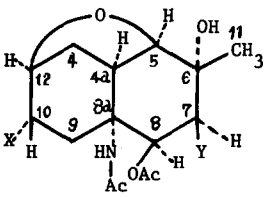
(XI) X=Y=OAc, Z=H
(mp 181-5°)

(XIV) X=Br, Y=H, Z=OH
(mp 187-8°dec.)

(XV) X=Br, Y=H, Z=OAc
(mp 194-5°dec.)

(XVI) X=Br, Y=OH, Z=H
(mp 188-9°dec.)

(XVII) X=Br, Y=OAc, Z=H
(mp 182-4°)



(XVIII) X=OAc, Y=OH
(mp 257-9°dec.)

(XIX) X=Y=OAc
(mp 212-3°)

NUMBERING IN THE FORMULAS IS CORRESPONDING TO THAT OF TETRODOTOXIN (I)

was then converted to an acetate (XV).[12] Epimeric alcohol epoxide (XVI) and its acetate (XVII)[13] were obtained from XII by the following sequence of reactions: reduction of XII with sodium borohydride and epoxidation with m-chloroperbenzoic acid, followed by acetylation with acetic anhydride and pyridine. Because oxidation of XVI with chromic anhydride in pyridine gave the keto epoxide XIII, XVI is the epimer of XIV at C-8. From the analysis of the coupling constants of nmr spectra of XV and XVII, based on a molecular model, the structure of the acetate having a coupling constant $J_{7,8}$=6 is assigned to XV and the structure of the acetate having a coupling constant $J_{7,8}$=0 to XVII. Because the pattern of nmr spectrum of XI ($J_{7,8}$=0, δ_{4a}=3.38) is quite similar to that of XVII ($J_{7,8}$=0, δ_{4a}=3.46), but quite different from that of XV ($J_{7,8}$=6, δ_{4a}=2.45), the acetate XI must have the same configuration at C-8 as that of the acetate XVII.

The reason why the feature of reduction of IX is different from that of XIII might be attributed to the difference of the conformation involved in the reduction. Namely, the conformation concerned in the reduction of IX could be one in which the hydroxyl group at C-10 is rather axial, that will cause a serious shield of the inner side of the ketone by the methylene group at C-9, but the outer side of the ketone is not covered by the acetamido group (equatorial with respect to the cyclohexanone ring). On the other hand, the conformation concerned in the reduction of XIII could be one in which the bromine atom at C-10 is equatorial (otherwise the bulky bromine occupies 1,3-diaxial relationship with the acetamido group), that will give an open space in the inner side of the ketone, but the outer side of the ketone is rather covered by the acetamido group (more axial-like bond with respect to cyclohexanone ring) as well as the epoxide ring.

In order to synthesize a compound having the same six chiral centers on the cyclohexane ring as those of tetrodotoxin (I), the epoxide ring of XI must be opened by an inner side attack of a reagent to the C-7 position. The fact that the keto epoxide XIII was reduced with sodium borohydride from the inner side at C-8 position gives us a hope that this possibility might be realized. When the epoxide XI was treated with a mixture of sulfuric acid and acetic acid (1:1) at -20°, a single product (XVIII)[14] was produced. The product was quantitatively converted to the acetate XIX[15] by a treatment with acetic anhydride and pyridine. Nmr spectrum of the acetate XIX showed clearly that the configuration at C-7 is as shown in the formula XIX from the value of the coupling constants ($J_{7,8}$=4, $J_{5,7}$=1.2). Since the inversion at C-7 was involved in this reaction, the configuration of the hydroxyl group at C-6 must be same as that of the epoxide XI. This was further confirmed by a transformation of XVIII into the starting epoxide XI by successive treatments of XVIII with mesyl chloride/pyridine, potassium hydroxide in aq. dioxane, and acetic anhydride/pyridine.

We have developed a method synthesizing stereospecifically the compound having the same six chiral centers on the cyclohexane ring as those of tetrodotoxin and obtained enough evidence about the correctness of their stereochemistry. Further efforts for a synthetic approach towards tetrodotoxin are being made in our laboratories based on the direction described in this communication.

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REFERENCES AND FOOTNOTES

1. Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, and S. Sugiura, Tetrahedron Letters, 59, 5127 (1970)

2. Satisfactory analytical and spectroscopic data were obtained for all the new compounds.
3. III was quantitatively prepared from II with mesyl chloride/triethylamine.
4. ms 233(M^+); λ(MeOH) 238nm (ε 11,800); ν(KBr) 1688, 1635, 1537 cm^{-1}; δ(ppm:$CDCl_3$) 2.04(6H), 4.22(1H,dd,J=5,2), 5.4-5.9(2H), 6.62(1H,q,J=1.5)
5. ms 235(M^+); λ(MeOH) 227nm (ε 10,900); ν(KBr) 1681, 1639, 1550 cm^{-1}; δ(ppm:$CDCl_3$) 1.95(3H,s), 2.04(3H,d,J=1.5), 3.25(1H), 4.26(1H,d,J=4.5), 5.76(2H), 5.90(1H,q,J=1.5)
6. ms 251(M^+); λ(MeOH) 227nm (ε 13,200); ν(KBr) 1692, 1650, 1549 cm^{-1}; δ(ppm:$CDCl_3$) 1.88(3H,s), 2.01(3H,d,J=1.5), 3.77(1H,t,J=4.5), 4.20(1H,t,J=5), 4.32(1H,d,J=4.5), 5.03(1H), 5.84(1H,q,J=1.5)
7. VII was prepared by acetylation of VI with acetic anhydride/pyridine: δ(ppm:$CDCl_3$) C_4-H: 1.87 (ddd,J=13,4.5,3) and 2.38(d,J=13), C_4a-H: 3.77(t,J=3), C_5-H: 4.34(d,J=3), C_7-H: 5.86(q,J=1.5), C_9-H: 1.45(d,J=16)and 2.40(dd, J=16,4.5), C_{10}-H: 4.92(t,J=4.5), C_{11}-H: 2.07(d,J=1.5), C_{12}-H: 4.45(t,J=4.5), N-Ac and O-Ac: 2.04(s)
8. VIII was obtained by oxidation of VI with $CrO_3 \cdot 2py$ in CH_2Cl_2: δ(ppm:$CDCl_3$) C_4-H: 2.43(ddd,J=14,6,3.5) and 2.68(d,J=14), C_4a-H: 3.67(t,J=3.5), C_5-H: 4.53(d,J=3.5), C_7-H: 6.01(q,J=1.5), C_9-H: 2.29(d,J=17) and 3.07(d,J=17), C_{11}-H: 2.14(d,J=1.5), C_{12}-H: 4.39(d,J=6), N-Ac: 2.05(s)
9. The configuration at C-10 was assigned from the consideration that an epoxidation to the isolated double bond from the outer side of V occured and the resultant epoxide is attacked by the hydroxyl group at C-5 from the inner side in an intramolecular fassion.
10. ms 267(M^+); ν(KBr) 1725, 1649, 1540 cm^{-1}; δ(ppm:DMSO-d_6) 1.47(3H,s), 1.87(3H,s), 3.2(2H), 3.80(1H), 4.19(1H,t,J=6), 4.36(1H,d,J=4)
11. The same acetate was alternatively prepared by one of the following sequence of reactions: i), reduction of VI with sodium borohydride, epoxidation with m-chloroperbenzoic acid, and then acetylation with acetic anhydride/pyridine; ii), reduction of VI, acetylation, and then epoxidation: ms 353(M^+); ν(KBr) 1738, 1643, 1550, 1240 cm^{-1}; δ(ppm:$CDCl_3$) 1.50(3H,s), 1.95 (3H,s), 2.10(3H,s), 2.11(3H,s), 2.97(1H,d,J=1.2), 3.38(1H,t,J=4), 4.31(1H,dd,J=4,1.2), 4.40 (1H,t,J=6), 4.99(1H,t,J=6), 5.74(1H,s)
12. ms 333 and 331(M-42); ν(KBr) 1747, 1651, 1547, 1240 cm^{-1}; δ(ppm:$CDCl_3$) 1.47(3H,s), 1.97(3H,s), 2.05(3H,s), 2.45(1H,dd,J=4,5), 3.51(1H,dd,J=6,1.2), 4.20(1H,t,J=5), 4.30(1H,dd,J=4,1.2), 4.45 (1H,t,J=5), 5.42(1H,d,J=6)
13. ms 333 and 331(M-42); ν(KBr) 1753, 1656, 1553, 1215 cm^{-1}; δ(ppm:$CDCl_3$) 1.47(3H,s), 1.95(3H,s), 2.11(3H,s), 2.96(1H,d,J=1.2), 3.46(1H,t,J=4), 4.26(1H,t,J=4), 4.33(1H,dd,J=4,1.2), 4.45(1H, t,J=4), 5.78(1H,s)
14. ms 371(M^+), 353, 329, 311; ν(KBr) 1724, 1651, 1544, 1245 cm^{-1}
15. ms 413(M^+), 371, 353; ν(KBr) 1724, 1670, 1535, 1240 cm^{-1}; δ(ppm:$CDCl_3$) 1.34(3H,s), 1.91(3H,s), 2.01(3H,s), 2.03(3H,s), 2.21(3H,s), 3.42(1H,t,J=4), 3.70(1H,dd,J=4,1.3), 4.16(1H,t,J=6), 5.08 (1H,t,J=6), 5.20(1H,dd,J=4,1.3), 6.11(1H,d,J=4)