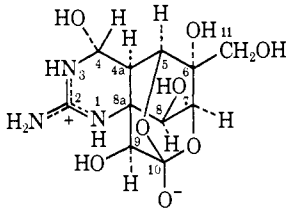
Communications to the Editor

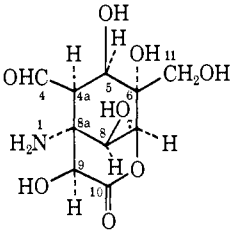
Synthetic Studies on Tetrodotoxin and Related Compounds. III.[1,2] A Stereospecific Synthesis of an Equivalent of Acetylated Tetrodamine

Sir:

In connection with investigations directed toward a total synthesis of tetrodotoxin **1**, we reported our basic plan to approach the toxin and the synthesis of some potentially useful intermediates.[1,3,4] In this communication we report a stereospecific synthesis of an equivalent, for synthetic purposes, of acetylated tetrodamine **2**.[5]

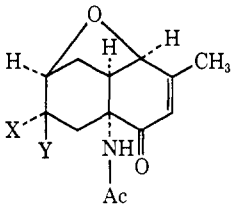


1, tetrodotoxin

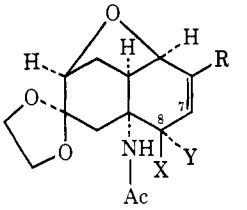


2, tetrodamine

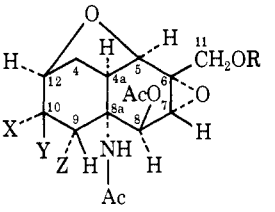
Oxidation of the ether alcohol **3**[1,6] with chromic anhydride in aqueous pyridine at 50° afforded the diketone **4**[7] (mp 167–168°) in 90% yield. Ketalization of **4** with ethylene glycol in methylene chloride containing a catalytic amount of boron trifluoride etherate gave quantitatively the monoketal **5**[7] (mp 214–216°). Meerwein–Ponndorf–Verley reduction of **5** gave exclusively[8] the alcohol **6**[7] (mp 198–199°), which was then converted to the acetate **7**[7] (mp 221–223°) after the usual manner (overall yield from **5**, >95%). The configuration of the newly introduced asymmetric center is expected to be the desired one, because the monoketal **5** is a cage-like molecule and hence an approach of the reducing reagent *from the outer side* is favorable. Indeed an analysis of the nmr spectrum of the acetate **7** and of the epimeric acetate **8**[7,9] (double mp 221–223° and 225–228° dec) supports the expectation. Namely, no spin–spin coupling between the protons at the 7 and 8 positions was observed in **7**,[10] while 6 Hz spin–spin coupling between these protons was observed in **8**.[10]



3, X = OH; Y = H
4, X = Y = O (ketone)
5, X = Y = 



6, X = OH; Y = H; R = CH_3
7, X = OAc; Y = H; R = CH_3
8, X = H; Y = OAc; R = CH_3
9, X = OAc; Y = H; R = CHO
10, X = OAc; Y = H; R = CH_2OH

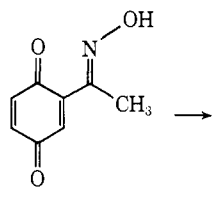


11, X = Y =  ; Z = H; R = H

12, X = Y =  ; Z = H; R = Ac

13, X = Y = O (ketone); Z = H; R = Ac
14, X = Y = OEt; Z = H; R = Ac
17, X = Y = O (ketone); Z = OAc; R = Ac

Selenium dioxide oxidation of the acetate **7** at 180° for 60 min in xylene afforded quantitatively the aldehyde **9**[7] [mp 208–211°; nmr ($CDCl_3$) 9.74 (1 H, s)], which was reduced quantitatively to the corresponding alcohol **10**[7] (mp 236–237°) by sodium borohydride in methanol and dioxane at 0°. The double bond in **10** was epoxidized with *m*-chloroperbenzoic acid (1.3 equiv) in ethylene dichloride containing a small amount of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol)[11] at 90°, to



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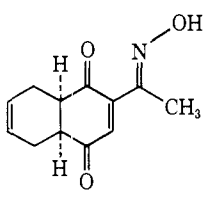
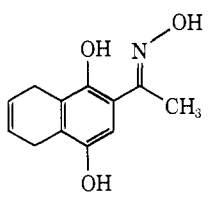


ii



iii

(1) Part II of this series: Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, and H. Kakoi, *Tetrahedron Lett.*, 5129 (1970).

(2) Presented to the 8th International Symposium of The Chemistry of Natural Products, New Delhi, India, Feb 1972.

(3) Y. Kishi, F. Nakatsubo, M. Aratani, T. Goto, S. Inoue, H. Kakoi, and S. Sugiura, *Tetrahedron Lett.*, 5127 (1970).

(4) In part I of this series, structure iii was assigned to the Diels–Alder adduct of the oxime i and butadiene *in the absence of stannic chloride*. However, structure iii must be corrected to structure ii from the results obtained in further studies. An acid treatment of the adduct ii (mp 161–163° dec) yielded iii (mp 183–186°).

(5) Although compound **2** or its equivalent—the alternative six-membered lactone or hemilactal or carboxylic acid—has not been derived from tetrodotoxin **1**, we designate it tetrodamine, because it or its equivalent is a key intermediate of tetrodotoxin synthesis.

(6) An alternative and superior method of synthesis of **3** has been developed and will be reported in due course.

(7) Satisfactory analytical and spectroscopic data were obtained on this compound.

(8) Reduction of **5** with sodium borohydride in methanol at 0° gave a mixture of epimeric alcohols in the ratio 4 (**6**):1 (alcohol corresponding to **8**).

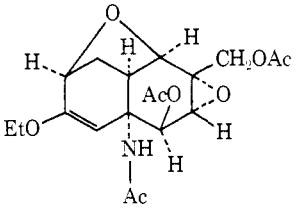
(9) Prepared from the epialcohol by acetylation; see ref 8.

(10) The dihedral angle between these protons is approximately 90° in **7** and 30° in **8**: A. A. Bothner-by and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961).

(11) For the effect of the addition of this reagent and the application of the procedure for epoxidation of olefins having poor reactivity, see Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *Chem. Commun.*, 64 (1972).

yield the epoxide **11**[7] (mp 212–213°) in 95% yield. Acetylation of the epoxide **11** in the usual way gave the acetate **12**[7] (mp 243–245°) quantitatively. Deketalization of **12** was brought about by aqueous trifluoroacetic acid at 70° for 30 min,[12] followed by acetylation with acetic anhydride and pyridine, to afford the keto-epoxide **13**[7] [mp 166–168°; nmr ($CDCl_3$) 1.91 (3 H, s), 2.10 (3 H, s), and 2.15 (3 H, s)] in 80% yield. The configurations of the 6, 7, and 8 positions in **13** were deduced from the analysis of the nmr spectrum, based on the fact that no spin–spin coupling between the protons at the 7 (δ 3.23 ppm) and 8 positions (δ 5.74 ppm) was observed.[13] More detailed arguments related to this point were given in our previous paper.[1]

Ketalization of the ketoepoxide **13** with ethyl orthoformate in ethanol containing a catalytic amount of camphorsulfonic acid at 80°,[12] followed by acetylation with acetic anhydride and pyridine, afforded the diethyl ketal **14**[7] (mp 143–144°). Refluxing **14** in purified *o*-dichlorobenzene yielded the enol ether **15**[7] (mp 227–228°), epoxidation of which with *m*-chloroperbenzoic acid in methylene chloride in the presence of suspended potassium carbonate[14] afforded the acid-labile epoxide **16**. The α configuration of the newly



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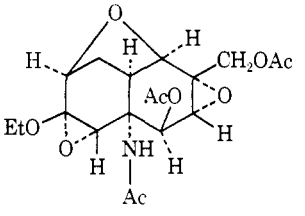
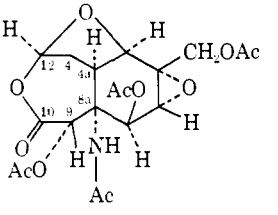


16

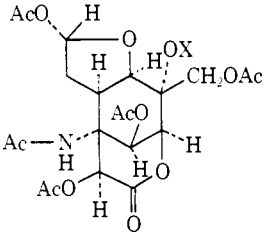
introduced epoxide ring was assigned from the consideration that the approach of the peracid to the double bond *from the* α *side* is favorable for steric reasons. Brief treatment of **16** with acetic acid at room temperature yielded exclusively the keto acetate **17**[7] [mp 179–182°; nmr ($CDCl_3$) 2.00 (3 H, s), 2.12 (3 H, s), 2.16 (3 H, s), and 2.30 (3 H, s)]. The overall yield from the ketoepoxide **13** to the keto acetate **17** was about 70%. The α configuration of the acetoxy group at C-9[15] was assigned from the consideration that the configuration of the epoxide ring was retained at the C-9 position in the acetolysis.[16] The conclusive evidence on the assignment is given later.

Baeyer–Villiger oxidation of the keto acetate **17** with *m*-chloroperbenzoic acid in methylene chloride at room temperature gave exclusively[17] the seven-membered lactone **18**[7] [mp 219–220°; nmr ($CDCl_3$) 2.01 (3 H, s), 2.15 (3 H, s), 2.17 (3 H, s), and 2.27 (3 H, s)] in quantitative yield. Structure **18** was confirmed by the nmr spectrum; namely, the signal of the proton at C-12 appears at 5.78 ppm in **18**, while the corresponding signal in **17** is found at 4.60 ppm.

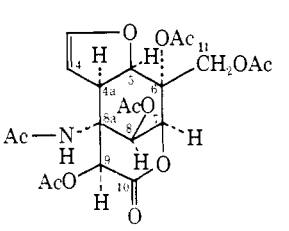


18

Treatment of **18** with potassium acetate in acetic acid at 90° for 2 hr yielded the six-membered lactone **19**[7] (mp 244° dec) in quantitative yield. The transformation of **18** to **19** involves opening of the seven-membered lactone group, to generate at one terminus a carboxylate group which attacks the epoxide ring by an intramolecular SN2 reaction, while at the other terminus the oxonium ion is attacked by acetate ion from the less hindered side. Acetylation of **19** with acetic anhydride containing a catalytic amount of camphorsulfonic acid at 100° afforded the hexaacetate **20**[7] [mp 256–258°; nmr ($CDCl_3$) 1.97 (3 H, s), 2.05 (3 H, s), 2.08 (3 H, s), 2.16 (6 H, s), and 2.34 (3 H,s)] in practically quantitative yield.



19, X = H
20, X = Ac



21

Pyrolysis of **20** under a high vacuum at 290–300° for a short time afforded the dihydrofuranacetamide **21**[7] [mp 196–199°; nmr ($CDCl_3$) 1.98 (3 H, s), 2.08 (3 H, s), 2.15 (3 H, s), 2.19 (3 H, s), and 2.26 (3 H, s)] in 80% yield. The presence of the dihydrofuran moiety in **21** was easily detected from the nmr spectrum; a four-spin system typical of the dihydrofuran moiety was observed at 6.39 (d of d, J = 2.5, 1.3 Hz), 5.28 (t, J = 2.5 Hz), 4.72 (d, J = 9 Hz), and 4.25 ppm (br

(12) Under these conditions a part of the acetyl group at the 11 position was hydrolyzed.

(13) The dihedral angle between these protons is approximately 90°; N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 99–102.

(14) In the absence of potassium carbonate, the compound bearing a *m*-chlorobenzoxy group in place of the acetoxy group at C-9 in 17 was isolated as the major product.

(15) The numbering in this paper corresponds to that of tetrodotoxin 1.

(16) The stereospecific transformation from **16** to **17** could be understood as depicted below. Concerning the opening of an epoxy ether with an organic acid, see C. L. Stevens and S. J. Dykstra, *J. Amer. Chem. Soc.*, 75, 5975 (1953).

(17) Extremely high selectivity of the migrating bond in the oxidation could be attributed to the effect of the ether linkage at the 12 position. In the compound bearing bromine or hydrogen in place of the acetoxy group at the 9 position, the same high selectivity was observed: Y. Kishi, M. Aratani, T. Fukuyama, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, unpublished results.

d, J = 9 Hz).[18] From a detailed examination of the nmr spectrum of **21**, the evidence on the configuration at the 9 position was obtained. Namely, a spin–spin coupling (1 Hz) was observed between the protons at C-9 and C-4a, but no spin–spin coupling was observed between the protons at C-9 and C-8. These observations are consistent with the fact that the protons at C-9 and C-4a are arranged in the configuration of the letter W, while the protons at C-9 and C-8 are not.[19]

The dihydrofuranacetamide **21** thus synthesized can be considered the equivalent of acetylated tetrodamine **2**, for synthetic purposes. Stereospecific total syntheses of DL-tetrodotoxin **1** from **21** will be described in the following communication.

Acknowledgment. Financial support from Matsunaga Science Foundation and Yamaji Foundation is gratefully acknowledged.

(18) L. M. Jackmann, "Applications of NMR Spectroscopy in Organic Chemistry," Pergamon Press, London, 1955, pp 87–88; T. Asao, G. Büchi, M. Abdel-Kader, S. B. Chang, E. L. Wick, and G. N. Wogan, *J. Amer. Chem. Soc.*, **87**, 882 (1965); R. K. Ness and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 435 (1963).

(19) Exactly similar phenomena were observed in the nmr spectra of tetrodotoxin derivatives. Furthermore, in the compound lacking an acetoxy group at C-9 in **21**, spin–spin couplings between the protons at C-9 and C-8, as well as the protons at C-9 and C-4a, were observed.

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Synthetic Studies on Tetrodotoxin and Related Compounds. IV.[1,2] Stereospecific Total Syntheses of DL-Tetrodotoxin

Sir:

In connection with investigations directed toward a total synthesis of tetrodotoxin **1**, we reported in the preceding paper[1] a stereospecific synthesis of an equivalent of acetylated tetrodamine. In this communication, we report two stereospecific conversions of the dihydrofuranacetamide **2**[1] into DL-tetrodotoxin **1**.

Osmium tetroxide oxidation of the dihydrofuranacetamide **2** in THF containing pyridine at −20° afforded the diol **3**[3a] (mp 174–177° dec), which was converted to the acetonideacetamide **4**[3a,4] [mp 256–259°; nmr ($CDCl_3$) 1.30 (3 H, s), 1.48 (3 H, s), 1.99 (3 H,s), 2.07 (3 H, s), 2.15 (3 H, s), 2.17 (3 H, s), and 2.32 (3 H, s)] in the usual way. The overall yield from **2** to **4** was 70%. A treatment of **4** with triethyloxonium tetrafluoroborate in methylene chloride in the presence of sodium carbonate at room temperature, followed by aqueous acetic acid work-up in methylene chloride, gave the acetonideamine **5**[3a,5] [mp 199–201°; nmr ($CDCl_3$) 1.34 (3 H, s), 1.51 (3 H, s), 2.06 (3 H, s), 2.11 (3 H, s), 2.22 (3 H, s), and 2.24 (3 H, s)] in 93% yield. Cyanogen bromide treatment[6] of **5** in the presence of sodium bicarbonate at 60° for 60 min afforded the cyanamide **6**[3b] [ir ($CHCl_3$) 2240 cm^{-1}], which was treated with hydrogen sulfide at 100° for 40 hr, to yield the thiourea **7**[3a] [mp 232–236° dec; nmr ($CDCl_3$–CD_3OD) 1.32 (3 H, s), 1.49 (3 H, s), 2.06 (3 H, s), 2.13 (3 H, s), 2.15 (3 H, s), and 2.24 (3 H, s)]. The overall yield from **5** to **7** was practically quantitative. The thiourea **7** was converted to the *N*-acetylethylisothiourea **8**[3b] by treatment with triethyloxonium tetrafluoroborate in methylene chloride, followed by acetylation with acetic anhydride and pyridine. The *N*-acetylethylisothiourea **8** was alternatively synthesized by treatment of the acetonideamine **5** with *S*,*S*-diethyl *N*-acetyliminodithiocarbonimidate[7] at 120° for 12 hr in one step. However, the yield through the thiourea **7** was better. Treatment of **8** with acetamide[8] at 150° for 60 min gave the diacetylguanidine acetonide **9**[3a] [mp 249–251° dec; nmr ($CDCl_3$) 1.30 (3 H, s), 1.50 (3 H, s), 2.05 (3 H, s), 2.08 (3 H, s), 2.10 (3 H, s), 2.14 (3 H, s), 2.17 (3 H, s), and 2.31 (3 H, s); uv (MeOH) 255 nm (log ϵ 4.18) and 222 (4.08)]. The overall yield from **5** to **9** was approximately 50%.[9]

Treatment of **9** with boron trifluoride in a mixture of trifluoroacetic acid and methylene chloride (3:10) at room temperature for 30 min afforded cleanly the diacetylguanidine diol **10**[3b] [amorphous solid; nmr ($CDCl_3$) 2.08 (3 H, s), 2.10 (3 H, s), 2.12 (3 H, s), 2.16 (3 H, s), 2.18 (3 H, s), and 2.33 (3 H, s); uv (MeOH) 255 and 222 nm] in approximately 60% yield.[10] The

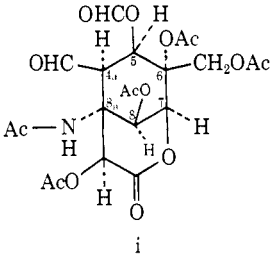
(1) Part III of this series: Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Amer. Chem. Soc.*, **94**, 9217 (1972).

(2) Presented at the 8th International Symposium of The Chemistry of Natural Products, New Delhi, India, Feb 1972.

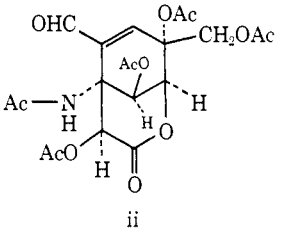
(3) (a) Satisfactory analytical and spectroscopic data were obtained on this compound. (b) Satisfactory spectroscopic data were obtained on this compound.

(4) The numbering in this paper corresponds to that of tetrodotoxin **1**.

(5) The protection of the dihydrofuran moiety in **2** as the acetonide group was carried out for the following reason. Namely, ozonolysis of **2** in methanol at −78°, followed by dimethyl sulfide work-up, gave the α,β-unsaturated aldehyde ii[3b] [nmr ($CDCl_3$) 9.66 (1 H, s)]. It was possible to detect the aldehyde i [nmr ($CDCl_3$) 8.22 (1 H, s) and 9.81 (1 H, s)] in the reaction mixture at low temperature by the nmr spectrum, but i could not be isolated. The extremely facile elimination of formic acid from i is readily understood, when one considers (a) stereochemistry at C-4a and C-5 is suitable for the elimination and (b) a heavy steric compression around C-5, C-7, and C-8a is released by the elimination. These results suggested that the aldehyde group at C-4a must be generated after the guanidino group had been introduced at the C-8a position.



i



ii

(6) Usual methods to convert amines to the corresponding guanidines were not applicable to **5**, because the lactone group as well as the acetyl groups are exceptionally labile to bases.

(7) H. L. Wheeler and H. F. Merriam, *J. Amer. Chem. Soc.*, **23**, 283 (1901).

(8) Attempts to convert the *N*-acetylethylisothiourea 8 or the corresponding ethylisothiourea into a guanidine derivative by treatment with ammonia or ammonium salts were unsuccessful—probably for the reason pointed out in ref 6.

(9) One of the by-products of this transformation was *N*-acetylurea.

(10) Attempts to convert the diacetylguanidine acetonide **9** to the monoacetylguanidine acetonide iii were not promising. For example, on heating **9** in absolute methanol at 100° for 20 min, the cyclic monoacetylguanidine derivative iv[3b] [nmr ($CDCl_3$) 1.29 (3 H, s), 1.47 (3 H, s), 2.07 (3 H, s), 2.10 (6 H, s), and 2.17 (3 H, s)] was obtained. On the