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

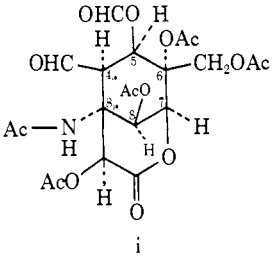
(1) Part III of this series: Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Amer. Chem. Soc.*, **94**, 9217 (1972).

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

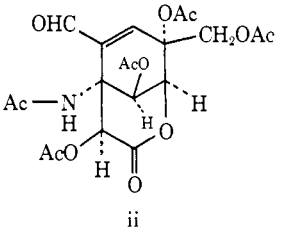
(3) (a) Satisfactory analytical and spectroscopic data were obtained on this compound. (b) Satisfactory spectroscopic data were obtained on this compound.

(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

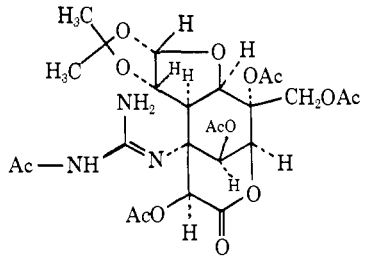
diacetylguanidine diol **10** was successfully converted to crystalline DL-tetrodotoxin **1** by the following three steps: (i) hydrolysis of the diacetylguanidino group to the monoacetylguanidino group under acidic conditions, *i.e.*, aqueous trifluoroacetic acid at 60° for 5 min,[10,11] (ii) cleavage of the diol group with periodic acid in aqueous methanol at 0°,[12] and (iii) hydrolysis of the acetyl groups with ammonium hydroxide in aqueous methanol at room temperature overnight.[13] The maximum yield from **10** to **1** was 15%.

Synthetic DL-tetrodotoxin was identified with natural tetrodotoxin by comparison of nmr spectra in D_2O containing a trace amount of trifluoroacetic acid, ir spectra,[14] and toxicity.[15]

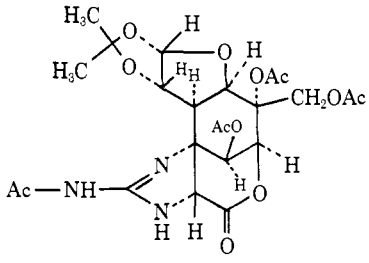
An alternative, more direct route to DL-tetrodotoxin **1** from the dihydrofuranacetamide **2** was established. Treatment of **2** with triethyloxonium tetrafluoroborate (excess)[16] in methylene chloride in the presence of sodium carbonate, followed by aqueous acetic acid work-up in methylene chloride, afforded the dihydrofuranamine **11**[3b] [amorphous solid; nmr ($CDCl_3$) 2.05 (3 H, s), 2.11 (3 H, s), 2.17 (3 H, s), and 2.19 (3 H, s)] in 92% yield. The dihydrofuranamine **11** was converted to the dihydrofuran *N*-acetylethylisothiourea **12**[3b] by heating **11** with *S,S*-diethyl *N*-acetyliminodithiocarbonimidate[7] at 120° for 12 hr. Heating **12** with acetamide at 150° for 60 min gave the dihydrofuran diacetylguanidine **13**[3a,17] [mp 230–232° dec; nmr ($CDCl_3$) 2.07 (3 H, s), 2.11 (6 H, s), 2.17 (6 H, s), and 2.28 (3 H, s); uv (MeOH) 259 nm (log ε 4.20)]. The overall yield from **2** to **13** was approximately 20%.[9]

In this series, the dihydrofuran monoacetylguanidine **14**[3b] [amorphous solid; nmr ($CDCl_3$) 2.02 (3 H, s), 2.08 (3 H, s), 2.15 (3 H, s), 2.16 (3 H, s), and 2.18 (3 H, s)] was obtained simply by treatment of **13** with ammonia in a mixture of methylene chloride and methanol (1:1) at room temperature.[18,19] Osmium tetroxide oxidation

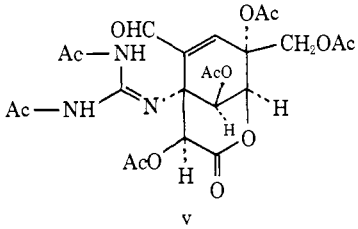
other hand, under acidic conditions, *e.g.*, aqueous trifluoroacetic acid at room temperature or camphorsulfonic acid in methanol at 100°, the desired monoacetylguanidine acetonide iii[3b] [nmr ($CDCl_3$) 1.28 (3 H, s), 1.48 (3 H, s), 2.03 (3 H, s), 2.07 (3 H, s), 2.10 (3 H, s), 2.13 (3 H, s), and 2.27 (3 H, s)] was obtained, but the yield was too low to continue further studies on this compound.



iii



iv



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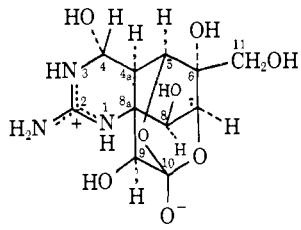
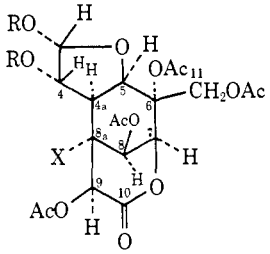
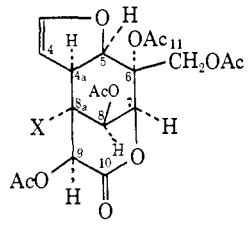


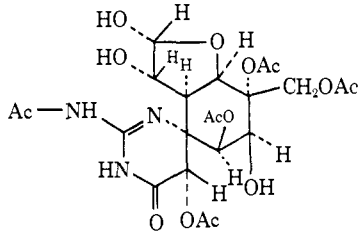
1, tetrodotoxin



3, R = H; X = NHAc
4, R = acetonide; X = NHAc
5, R = acetonide; X = NH_2
6, R = acetonide; X = NH–CN
7, R = acetonide; X = $NHC(=S)NH_2$
8, R = acetonide; X = N=C(SEt)NHAc
9, R = acetonide; X = N=C(NHAc)NHAc
10, R = H; X = N=C(NHAc)NHAc
15, R = H; X = $N=C(NH_2)NHAc$



2, X = NHAc
11, X = NH_2
12, X = N=C(SEt)NHAc
13, X = N=C(NHAc)NHAc
14, X = $N=C(NH_2)NHAc$



16

(11) The product at this stage was possibly the monoacetylguanidine diol **15**, but by this procedure it was impossible to isolate this product. For the properties of **15**, see the second route.

(12) Sodium periodate oxidation of **10** gave the α,β-unsaturated aldehyde v[3b] [nmr ($CDCl_3$) 1.90 (3 H, s), 2.07 (3 H, s), 2.12 (3 H, s), 2.17 (6 H, s), 2.21 (3 H, s), and 9.47 (1 H, s)]; see ref 5.

(13) At this stage crystalline tetrodotoxin **1** separated out from the solution; the method is that used to hydrolyze the acetyl groups of tetrodotoxin acetates; see T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, **21**, 2059 (1965).

(14) The ir spectrum of DL-tetrodotoxin in a KBr disk was found to be identical with that of natural tetrodotoxin.

(15) A detailed study of the toxicity of synthetic tetrodotoxin will be reported elsewhere.

(16) Triethyloxonium tetrafluoroborate in this experiment must be freshly prepared.

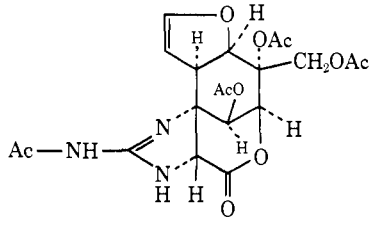
(17) Osmium tetroxide oxidation of **13** afforded the diacetylguanidine diol **10**, which was identified with the material synthesized by the first route.

of **14** in THF at −20° gave the monoacetylguanidine diol **15** [uv (MeOH) 240 nm]. The monoacetylguanidine diol **15** thus obtained was rather unstable; namely it isomerizes to the diacylguanidine diol **16** [uv (MeOH) 256 nm] on silica gel tlc or under basic conditions.[20] Sodium periodate oxidation of **15** in aqueous THF at 0° for 30 min, followed by quenching the oxidant with ethylene glycol, and then ammonium hydroxide hydrolysis in aqueous methanol,[13] afforded crystalline DL-tetrodotoxin **1**, which was identified with natural tetrodotoxin by comparison of spectroscopic data (nmr and ir[14]) and toxicity.[15] The overall yield from **13** to **1** by this route was around 25%.

Compared with the first route, the second one was better both in the overall yield from **2** and in reproducibility.

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

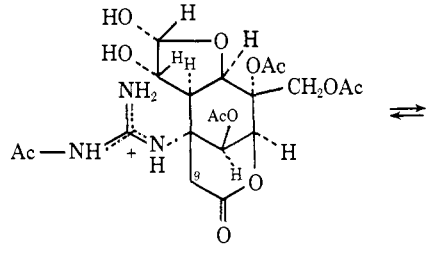
(18) One of the by-products of this step was the cyclic monoacetylguanidine vi[3b] [nmr ($CDCl_3$) 2.02 (6 H, s), 2.04 (3 H, s), and 2.12 (3 H, s)].



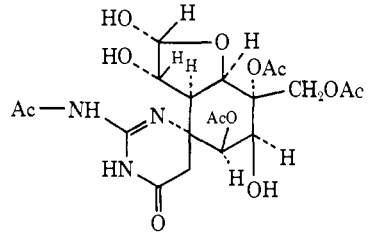
vi

(19) Ozonolysis of **14** under neutral or acidic conditions was not promising.

(20) In the 9-deoxy series (lacking acetoxy group at C-9), the compound vii corresponding to **15** was present under acidic conditions and the compound viii corresponding to **16** was present under neutral and basic conditions.



vii



viii

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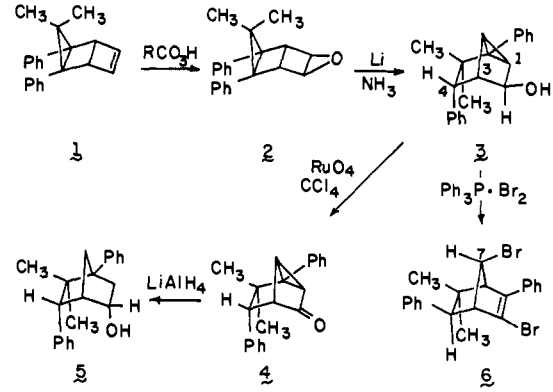
Intramolecular Epoxide Cleavage by Dissolving Metal Reduction of Proximal Cyclopropane Rings

Sir:

Recent research has revealed that phenyl substitution of cyclopropane rings is sufficient to promote their ready cleavage under conditions of alkali metal reduction.[1,2] The chief mechanistic question at issue has been evaluation of the extent to which stereoelectronic and steric factors control the stereospecificity of the observed ring openings. The latent chemical reactivity of the radical anions or dianions produced under these conditions has not heretofore been explored. The present work illustrates a synthetic application of this reduction which provides a novel synthetic entry to functionalized derivatives of strained tricyclic hydrocarbons.

When epoxide **2**, mp 71–72.5°,[3] readily available from *m*-chloroperbenzoic acid oxidation of tricycloheptene **1**,[4] was allowed to react with 2 equiv of lithium in liquid ammonia, alcohol **3** (mp 121–123°; ν_{max}^{KBr} 3300 cm^{-1})[3] was obtained in 90% yield. Its nmr spectrum ($CDCl_3$, 60 MHz) includes singlets at δ 1.02 and 0.88 (3 H each, methyls), multiplets at 7.2 (10 H), 3.13 (2 H), 2.58 (2 H), and 1.88 (1 H), and a particularly revealing doublet (J = 3.7 Hz) for the >C*H*OH proton at 4.55. The tricyclic structural assignment to **3** follows convincingly from appropriate Eu(fod)$_3$ shifting of the above spectrum,[5] high-yield (96%) ruthenium tetroxide oxidation[7] to ketone **4**, mp 117–118°,[3,8] and subsequent hydride reduction of **4** to *endo*-norbornanol **5**, mp 142.5–144.5°.[3,9]



(1) H. M. Walborsky, M. S. Aronoff, and M. S. Schulman, *J. Org. Chem.*, **36**, 1036 (1971), and relevant references cited therein.

(2) For an excellent comprehensive review of this field, see S. M. Staley, *Selec. Org. Transform.*, **2**, 309 (1972).

(3) Satisfactory (±0.3%) combustion data and mass spectral results were obtained for all new compounds. In those cases where the nmr spectra are not explicitly given, full agreement with the structural assignment was evidenced.

(4) L. A. Paquette and L. M. Leichter, *J. Amer. Chem. Soc.*, **92**, 1765 (1970); **93**, 5128 (1971).

(5) The relevant ΔEu values[6] are: H_1, −4.26; H_2, −11.53; H_3, −7.93; H_4, −2.37; H_7, −5.97.

(6) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734 (1970).

(7) H. Nakata, *Tetrahedron*, **19**, 1959 (1963); R. M. Moriarty, H. Gopal, and T. Adams, *Tetrahedron Lett.*, 4003 (1970); H. Gopal, T. Adams, and R. M. Moriarty, *Tetrahedron*, **28**, 4259 (1972).

(8) $\lambda_{max}^{CH_3CN}$ 228 (ϵ 1740), 252 (350), 258 (435), and 265 nm (340); $\delta_{TMS}^{CDCl_3}$ 7.32 (s, 10, aryl), 3.42 (m, 3), 3.1 (m, 1), 0.94 (s, 3), and 0.70 (s, 3). For a leading reference to conjugative effects in cyclopropyl carbonyl compounds, consult: A. Padwa, L. Hamilton, and L. Norling, *J. Org. Chem.*, **31**, 1244 (1966).

(9) $\delta_{TMS}^{CDCl_3}$ 7.2–7.6 (m, 10, aryl), 4.48 (m, 1), 3.2 (m, 1), 2.9 (m, 1), 1.55–2.25 (m, 5), 1.15 (s, 3), and 0.88 (s, 3). This reduction may be considered analogous to that of the double bond in α,β-unsaturated