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SYNTHETIC STUDIES ON TETRODOTOXIN AND RELATED COMPOUNDS. V.[1]

THE PROTECTING GROUP OF THE C_9-HYDROXY GROUP

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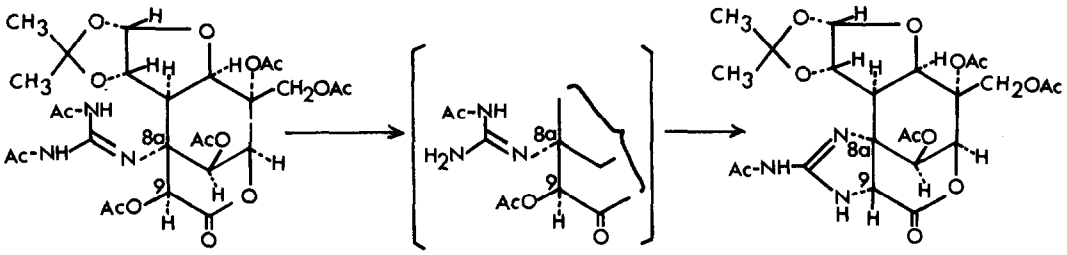
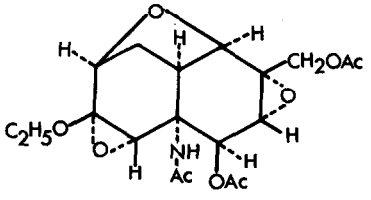
One of the difficulties in our first and second total synthesis[1] of tetrodotoxin was how to avoid formation of a cyclic monoacetylguanidino group from the C_{8a}-monoacetylguanidino and C_9-acetoxy groups. For instance, when the diacetylguanidine acetonide 1 was treated with methanolic ammonia in methylene chloride at room temperature, only one isolable product was the useless cyclic monoacetylguanidine acetonide 3,[1] which was presumably derived from 2 by an intramolecular substitution reaction. With a hope that a modification of the protecting group of the C_9-hydroxy group may eliminate the undesired substitution reaction, C_9-anisoate, C_9-m-chlorobenzoate, C_9-acetate, C_9-methoxyacetate, and C_9-ethyl carbonate derivatives of the dihydrofuran diacetylguanidine (7) have been prepared and a tendency of formation of the cyclic monoacetylguanidine has been examined.



1 2 3

Treatment of the ethoxy epoxide 4[2] in methylene chloride with 1N hydrochloric acid (a heterogeneous reaction) at room temperature gave the α-ketol 5[3a] (mp 171-4°C) in 60% yield. The α-ketol 5 was acylated to the keto-C_9-anisoate 6a[3a] (anisoyl chloride and sodium hydride in THF; mp 235-7°C), the keto-C_9-m-chlorobenzoate 6b[3a,4] (m-chlorobenzoyl chloride and sodium hydride in THF; mp 204-6°C), the keto-C_9-acetate 6c[2,3a] (acetic anhydride and pyridine; mp 179-182°C), the keto-C_9-methoxyacetate 6d[3b] (methoxyacetic anhydride and pyridine; mp 82-5°C), and the keto-C_9-ethyl carbonate 6e[3a] (ethyl chlorocarbonate and sodium carbonate in acetone; mp 202-5°C). Incidentally, the acetate 6c and the methoxyacetate 6d could be directly prepared by acetolysis[2] of 4 with acetic acid or methoxyacetic acid at room temperature, but the acid degradation reaction of 4 with anisic acid or m-chlorobenzoic acid was not as clean as with acetic acids.

By the method established before,[1,2] 6a, b, c, d, and e were transformed into the corresponding dihydrofuran diacetylguanidine derivative 7a[3a,5] (mp 214-6°C), 7b[3b] (crystalline solid), 7c[1,3a] (mp 230-2°C), 7d[3a] (mp 198-200°C), and 7e[3b] (crystalline solid) in seven steps respectively.



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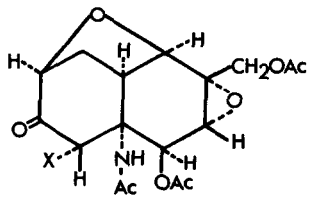


5 : X = OH

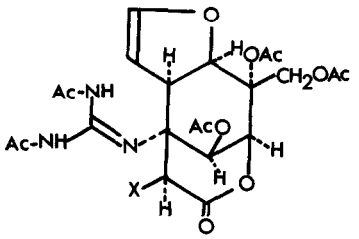
6a : X = p-$CH_3OC_6H_4$-CO_2

6b : X = m-ClC_6H_4-CO_2

6c : X = CH_3-CO_2

6d : X = CH_3OCH_2-CO_2

6e : X = C_2H_5O-CO_2



7a : X = p-$CH_3OC_6H_4$-CO_2

7b : X = m-ClC_6H_4-CO_2

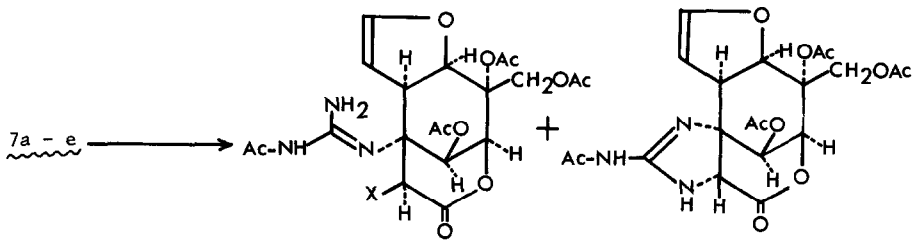
7c : X = CH_3-CO_2

7d : X = CH_3OCH_2-CO_2

7e : X = C_2H_5O-CO_2

The dihydrofuran diacetylguanidine 7a, b, c, d, and e were treated with a mixture (1 : 1) of methanolic ammonia (saturated at 0°C) and dry methylene chloride at room temperature for 15 minutes and the product(s) was isolated with a preparative tlc (silica gel). The results were summarized in the Table.

Table



8a - e 9

7a : X = p-$CH_3OC_6H_4$-CO_2	8a[6] : 100 %	9 : 0 %
7b : X = m-ClC_6H_4-CO_2	8b : 0 %	9[7] : 100 %
7c : X = CH_3-CO_2	8c[8] : ca. 70 %	9[7] : ca. 30 %
7d : X = CH_3OCH_2-CO_2	8d : 0 %	9[7] : 100 %
7e : X = C_2H_5O-CO_2	8e : 0 %	9[7] : 100 %

The results in the Table may suggest that one of the important factors controlling formation of the cyclic monoacetylguanidine 9 relates to the dissociation constant of the leaving acids in the substitution reaction --- compare the a series with the b series, and the c series with the d series. However, more extensive studies may be required to draw the conclusion.

It is important for the synthetic purposes that formation of the useless cyclic monoacetylguanidine 9 is completely avoided in the case of the anisoate series. Isolated dihydrofuran monoacetylguanidine C_9-anisoate 8a[3a,6] (mp 224-5°C dec.) turned out to be stable under basic (triethylamine) or acidic (camphorsulfonic acid in methylene chloride) conditions and could be well characterized.

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REFERENCES AND FOOTNOTES

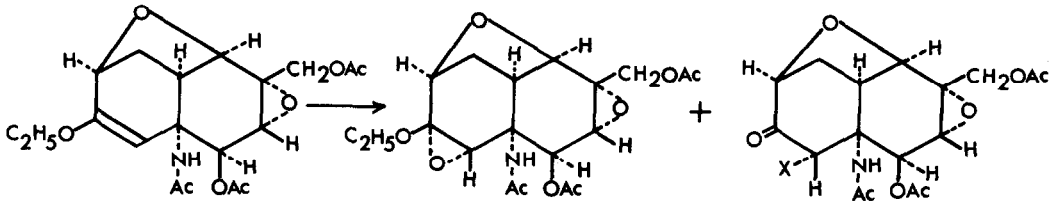
1. Part IV of this series: Y. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, J. Am. Chem. Soc., 94, 9219 (1972).

2. Y. Kishi, M. Aratani, T. Fukuyama, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, J. Am. Chem. Soc., 94, 9217 (1972).

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

b. Satisfactory spectroscopic data including mass spectra were obtained on this compound.

4. The by-product 6b (yield: <3%) of epoxidation (m-chloroperbenzoic acid and potassium carbonate in CH_2Cl_2)[2] of the enol ether 10 was utilized in the actual studies.



10 4 (yield: >95 %) 6b (yield: <3 %)

X = m-$ClC_6H_4CO_2$

5. $\delta_{ppm}^{CDCl_3}$ 2.11 (3H,s), 2.12 (3H,s), 2.16 (3H,s), 2.18 (3H,s), 2.23 (3H,s), 3.95 (3H,s), 7.10 (2H,AB,J=9Hz), and 8.18 (2H,AB,J=9Hz).

6. $\delta_{ppm}^{CDCl_3}$ 2.02 (3H,s), 2.07 (3H,s), 2.13 (3H,s), 2.17 (3H,s), 3.86 (3H,s), 6.92 (2H,AB,J=9Hz), and 7.95 (2H,AB,J=9Hz); λ_{max}^{MeOH} 245nm (log ε=4.37), 257 (4.32), and 272sh (4.15): $\lambda_{max}^{MeOH-H^+}$ 262nm (log ε=4.28), and 272sh (4.18).

7. mp 136-9°C; $\delta_{ppm}^{CDCl_3}$ 2.10 (3 3H,s), and 2.20 (3H,s); λ_{max}^{MeOH} 241nm (log ε=4.23): $\lambda_{max}^{MeOH-H^+}$ end absorption.

8. The compound 8c gradually cyclizes to the cyclic monoacetylguanidine 9 in methanol at room temperature or on tlc (silica gel).