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AMINODESOXYTETRODOTOXIN

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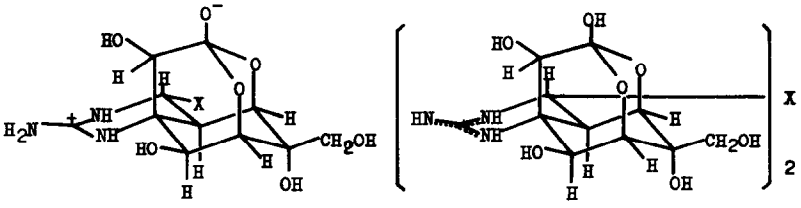
IN the previous communication (1), we deduced the structure of tetrodotoxin (I) and aminodesoxytetrodotoxin (II) as Ia and IIa, respectively. However, Tsuda et al. (2) recently reported that tetrodaminotoxin, which must be identical with II, exists in a dimeric form IIb, $C_{22}H_{33}O_{14}N_7$, and suggested also a dimeric form Ib for tetrodotoxin itself for the reason that they have similar physical properties (NMR, IR, X-ray powder diffraction, etc.).



Ia (X = OH) Ib (X = O)
IIa (X = NH_2) IIb (X = NH)

Previously we reported that tetrodotoxin exists in a monomeric form (C_{11}-compound) at least in solutions (1). In this communication, we give evidence indicating that aminodesoxytetrodotoxin is also monomeric C_{11}-compound. Then, there remains no reason to consider tetrodotoxin as the dimeric form Ib even in a solid state.

Aminodesoxytetrodotoxin, which is obtained by treatment of pentaacetylanhydroepitetrodotoxin p-toluenesulfonate (3) with concd. aqueous ammonia, exists in two forms, IIA and IIB, which are convertible

to each other by dissolving it in acid and precipitating it with ammonia, and can be distinguished by their infrared spectra; the former spectrum being very similar to that of the toxin (I).

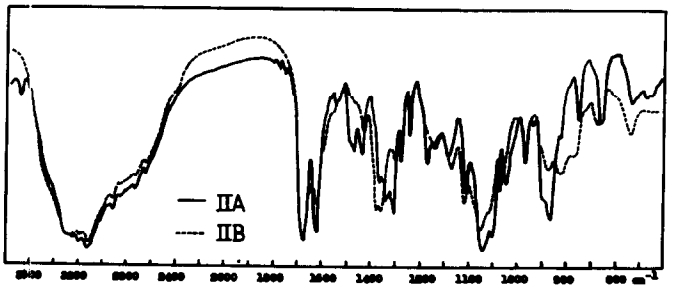


FIG. 1.
Infrared spectra of aminodesoxytetrodotoxin (IIA) and (IIB) in KBr

Analysis of II* (dried in vacuo at 80° for 20 hrs.).
Found (IIA): C, 40.46,40.77; H, 5.93, 5.95; N, 17.20, 17.14.
Found (IIB): C, 41.02, 41.01; H, 5.97, 5.88; N, 16.79, 17.08.
Calcd. for $C_{11}H_{18}O_7N_4.1/2H_2O$: C, 40.36; H, 5.85; N, 17.12.
Calcd. for $C_{22}H_{33}O_{14}N_7$: C, 42.41; H, 5.33; N, 15.83.

Amino derivative II has two pKa' values at 4.01 and 8.66 corresponding to the amino and the acidic ortho-ester group, respectively.** The titration equivalents of these two groups were equal (ca. 340) indicating that II is the monomeric C_{11}-compound (M.W. 327.29) and not the dimeric C_{22}-form, since it were the dimeric form, the titration equivalent corresponding to the pKa' 8.66 must be twice as much as that for the pKa' 4.01. The titration curve fits well a theoretical curve for the structure IIa (Fig. 2).

* The difference between the reaction conditions for preparation of aminodesoxytetrodotoxin and anhydroepitetrodotoxin is very slight (1) and the former is often contaminated by the latter, that lowers the nitrogen content of the former; for example, a sample showed the following analytical values: C, 40.61, 40.82; H, 6.24, 6.40; N, 15.96, 16.09.

** A pKa for the guanidine group must be present, but insolubility of II in basic solutions prevented the titration above pH 9.

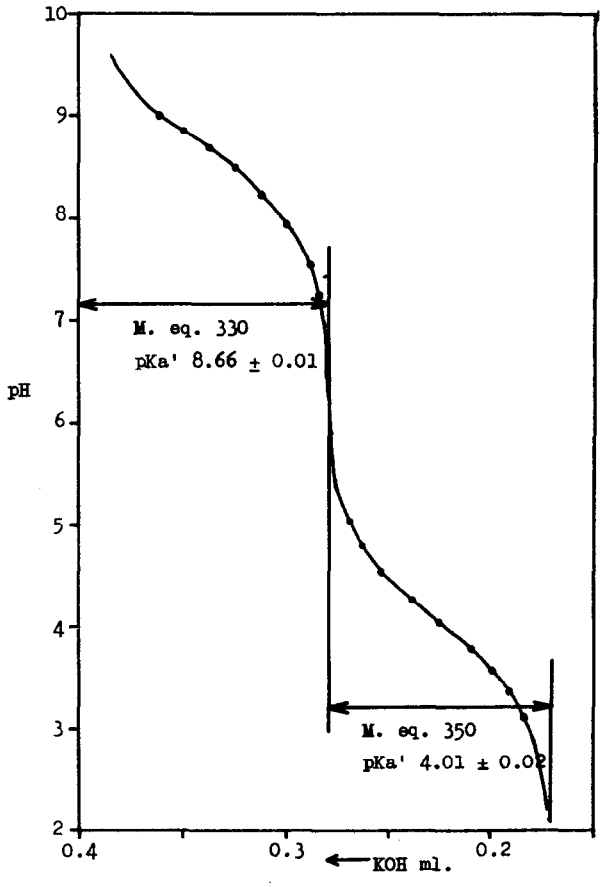


FIG. 2.
Titration curve of aminodesoxytetrodotoxin (IIA)*

Though Tsuda et al. (2) reported that tetrodaminotoxin can be converted to tetrodotoxin by heating with 10% hydrochloric acid, aminodesoxytetrodotoxin was recovered unchanged when having been refluxed with 2 N sulfuric acid or hydrochloric acid for 2 hrs.

* 3.201 mg. of IIA in 2.00 ml. of 0.020 N HCl was titrated with 0.100 N KOH. IIB showed a curve identical with that of IIA. The pKas were calculated from the observed values (black dots).

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REFERENCES

1. T. Goto, Y. Kishi, S. Takahashi and Y. Hirata, Tetrahedron Letters 779 (1964).
2. Tsuda, Lectured at Annual Meeting of Pharm. Soc. Japan, April 7, 1964 (Tokyo); K. Tsuda, R. Tachikawa, K. Sakai, C. Tamura, O. Amakasu, M. Kawamura and S. Ikuma, Presented at IUPAC Symposium on the Chemistry of Natural Products, April 13, 1964 (Kyoto); Chem. Pharm. Bull. (Japan) in Press, we are indebted to professor Tsuda for giving us a copy of the manuscripts before publication.
3. Also from other derivatives of tetrodotoxin; see ref. 1.