Structure of the C_8-Base, an Acid Degradation Product of Tetrodotoxin

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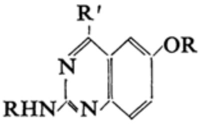
Alkaline degradation of tetrodotoxin⁽¹⁾ (swell-fish poison) afforded a yellow compound (C_9-base), whose structure was reported in the previous communication⁽²⁾. Tetrodotoxin also gave another yellow compound (C_8-base) when treated with sulfuric acid. That the C_8-base is 2-amino-6-hydroxyquinazoline (I) is deduced from the following evidences.



(II) R=R′=H
(II) R=CH_3CO, R′=H
(III) R=H, R′=CH_3

Tetrodotoxin was dissolved in concentrated sulfuric acid and the solution allowed to stand at room temperature for three days. Then the reaction mixture was neutralized with aqueous barium hydroxide and filtered. The filtrate was acidified with hydrochloric acid, evaporated to dryness under vacuum, and the residue was sublimed to give the C_8-base hydrochloride, m. p. over 250°C (in a sealed tube). Treatment of the hydrochloride with acetic andydride and pyridine afforded the diacetate (II), m. p. 198°C (in a sealed tube), $C_8H_5ON_3(COCH_3)_2$ (Found: C, 58.64; H, 4.55; N, 17.31. Calcd.: C, 58.77; H, 4.52; N, 17.14%); $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 248 (4.3), $\lambda_{\max}^{\mathrm{NaOH\text{-}EtOH}}$ 258 (4.1); ν_{KBr} 1745 (phenol ester), 1675 cm^{-1} (amide).

2-Amino-4-methyl-6-hydroxyquinazoline (III) was synthesized for comparison of its ultraviolet spectrum with that of the C_8-base. 2-Nitro-5-hydroxyacetophenone⁽³⁾, m. p. 146～147°C, was reduced catalytically (H_2/PtO_2) to give 2-amino-5-hydroxyacetophenone, m. p. 183～187°C (decomp.), which was then condensed with cyanamide. The quinazoline III thus obtained was converted to its hydrochloride, m. p. over 250°C (in a sealed tube). The ultraviolet spectrum of the C_8-base hydrochloride [$\lambda_{\max}^{H_2O}$ mμ (log ε): 233 (4.3), $\lambda_{\max}^{\mathrm{NaOH}}$ 245 (4.4)] was almost superimposable with that of the quinazoline III hydrochloride [$\lambda_{\max}^{H_2O}$ mμ (log ε): 233 (4.3), $\lambda_{\max}^{\mathrm{NaOH}}$

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1) H. Kakisawa, Y. Okumura and Y. Hirata, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1483 (1959).

2) T. Goto, Y. Kishi and Y. Hirata, This Bulletin, **35**, 1045 (1962); K. Tsuda et al. also reported the same conclusion, *Chem. Pharm. Bull.*, **10**, 247 (1962).

3) A. R. Osborn and K. Schofield, *J. Chem. Soc.*, **1955**, 2100.

245 (4.4)]. For a methyl substituent at C_4-position would not contribute much to the ultraviolet spectrum of the quinazoline III, the C_8-base must have the structure I. The NMR spectrum of C_8-base in deuterium oxide shows only three signals (all singlets) at -2, -23 and -73 c. p. s.[4] (area ratio 1 : 2 : 1), which were assigned to one proton at C_4, two at C_7 and C_8, and one at C_5, respectively.

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[4] Spectrum was taken on a Nihondenshi JM (40 Mc.) spectrometer using D_2O containing NaOD as solvent, and external benzene as a reference (0 c. p. s.).