Tetrahedron Letters No. 7, pp 627 - 630, 1977. Pergamon Press. Printed in Great Britain.

A PROMISING CYCLIZATION REACTION TO CONSTRUCT THE SAXITOXIN RING SYSTEM

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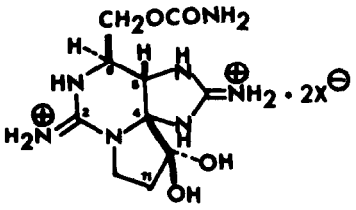
(Received in USA 8 December 1976; received in UK for publication 12 January 1977)

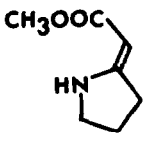
Saxitoxin 1 is the neurotoxin isolated from Alaska butter clams (Saxidomus giganteus), toxic mussels (Mytilus californianus), and axenic cultures of Gonyaulax catenella and is one of the most toxic nonprotein substances known.[1] The structure of saxitoxin was established by x-ray crystallography.[2,3] The toxin was also found in aged extracts of scallops collected during a Gonyaulax tamarensis bloom.[1] Three new toxins in addition to saxitoxin were isolated from soft shell clams, Mya arenaria, collected during red tide blooms on the New England coast.[4] Two of the three new toxins were shown to be 11α- and 11β-hydroxysaxitoxins (gonyautoxin II and III).[5] In this communication we wish to report an efficient cyclization reaction to construct the tricyclic ring system present in the saxitoxin structure.

Condensation of the vinylogous carbamate 2[6,7] (mp 100-1°) with acetaldehyde and isocyanic acid in ether at room temperature afforded the 2-oxo-dihydropyrimidine 3[7] [mp 140-1°; λ_{max}^{MeOH} 289 nm (ε 10,500); $\delta_{ppm}^{CDCl_3}$ 1.28 (3H, d, J=7 Hz), 2.00 (2H, quintet, J=7 Hz), 3.10 (2H, m), 3.71 (3H, s), 3.71 (2H, t, J=7 Hz), 4.40 (1H, m), 5.1 (1H, broad s)] in 72% yield. The structure of 3 was confirmed by the following experiments. Aqueous sodium hydroxide treatment of 3 in methanol at room temperature yielded the acid 4[7] (mp 194-5°dec.) in 88% yield. Pyrolysis (220°/5 min./N_2) of 4 gave an unstable dihydropyrimidine 5[7]. Permanganate oxidation of 5 afforded the known 2-oxo-pyrimidine 6[7] (mp 101-2°), one of the degradation products of saxitoxin.[8] Physical properties (mp, uv, nmr) of synthetic substance were consistent with those reported for 6.[8]

The acid 4 was converted into the urea 7[7] [mp 239-240°; λ_{max}^{MeOH} 258 nm (ε 5,900); $\delta_{ppm}^{CD_3OD}$ 1.24 (3H, d, J=7 Hz), 1.92 (2H, quintet, J=7 Hz), 2.56 (2H, t, J=7 Hz), 3.55 (2H, t, J=7 Hz), 4.16 (1H, q, J=7 Hz)] by four steps [1. $(COCl)_2$, 2. LiN_3, 3. Δ, 4. NH_3] in 65% overall yield. The urea 7 cyclized exclusively to the tricyclic urea 8[7] [mp 293-4° dec.; 93% yield; $\delta_{ppm}^{CD_3OD}$ 1.20 (3H, d, J=7 Hz), 2.0 (4H, m), 3.4 (4H, m)] in acetic acid at 50°.[9] The stereochemistry of 8 was determined by analysis of the nmr spectrum of the tri-N-methyl derivative[7,10] [mp 157-8°; $\delta_{ppm}^{CDCl_3}$ 1.12 (3H, d, J=7 Hz), 2.1 (4H, m), 2.77 (3H, s), 2.79 (3H, s), 2.84 (3H, s), 3.32 (1H, q, d, J=7, 1 Hz), 3.51 (1H, d, J=1 Hz), 3.6 (2H, m)] of 8. The spin-spin coupling constant (1 Hz) between the protons at the 5 and 6 positions is almost the same as that (1.3 Hz) of saxitoxin.[11] Cyclization of 7 in neat trifluoroacetic acid at room temperature yielded a 2:3 mixture of the tricyclic urea 8 (30% yield) and its epimer 9[7] [mp 307-9°; 45% yield; $\delta_{ppm}^{CD_3OD}$ 1.17 (3H, d, J=7 Hz), 2.1 (4H, m), 3.4 (3H, m), 4.02 (1H, d, J=3.5 Hz)].[12] The stereochemistry of 9 was also determined by analysis of the nmr spectrum; $J_{5,6}$ in this case is 3.5 Hz.



1 : Saxitoxin



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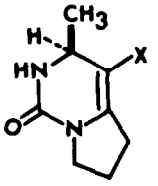
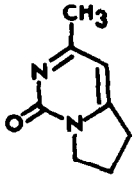


3 : X=CO_2CH_3

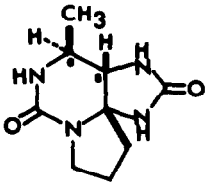
4 : X=CO_2H

5 : X=H

7 : X=$NHCONH_2$



6



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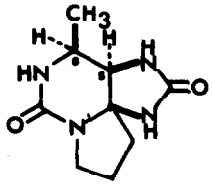
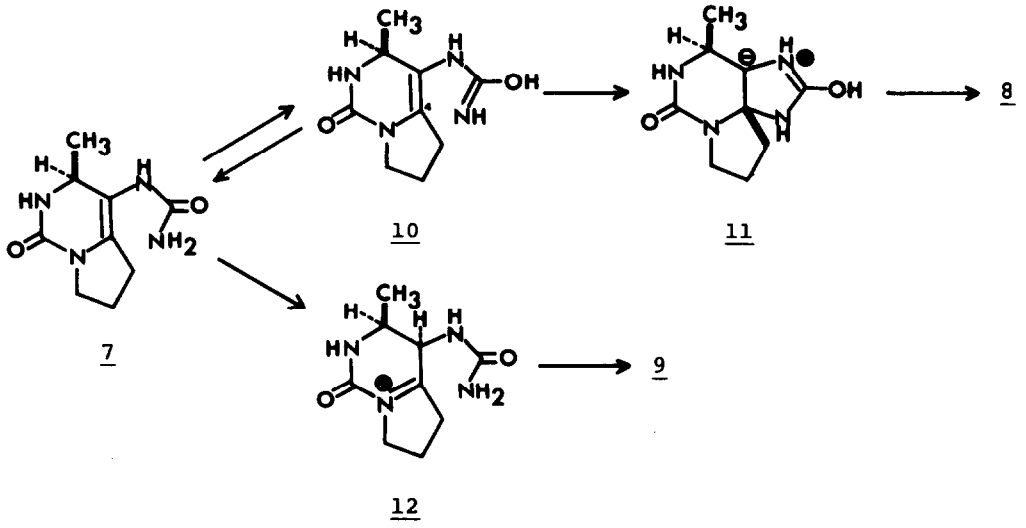


9

The tricyclic ureas 8 and 9 were not interconvertible under the trifluoroacetic acid or acetic acid conditions. These results suggest that two different processes of cyclization are operating. Acetic acid could catalyze the enolization of 7 into 10, which then cyclizes to the zwitter ion 11. In the 10⟶11 process, the urea group would be expected to approach the 4 position from the α side for steric reasons to yield 11, protonation-deprotonation of which yields the tricyclic urea 8. Supporting evidence for this proposed electrocyclization process is the fact that treatment of 7 with triethyloxonium tetrafluoroborate in methylene chloride in the presence of sodium carbonate at room temperature yields the di-O-ethyl derivative[7] (amorphous solid) of the tricyclic urea 8. In strong acidic media such as trifluoroacetic acid, protonation of the unsaturated urea system of 7 might be taking place, followed by a cyclization process. The reason why a 2:3 mixture of 8 and 9 is produced in a strong acidic medium is not clear at this point. This could be due to a non-stereospecific protonation of 7 or the operation of both proposed processes in trifluoroacetic acid.



The stereospecific cyclization reaction of 7 into 8 has recently been extended to a total synthesis of d,l-saxitoxin in our laboratories.[13]

Acknowledgement. Financial assistance from National Institutes of Health, Milton Fund, Hoffmann-La Roche Company, and Astra Pharmaceutical Products is gratefully acknowledged.

References and Footnotes

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6. In studies related to the total syntheses of vitamin B_{12}, the chemistry of this type of compounds was extensively investigated; for example, see A. Eschenmoser, Pure and Applied Chemistry, 7, 297 (1963), Quart. Rev., 24, 366 (1970) and references cited therein.
7. Satisfactory spectroscopic data (nmr, ms, ir, uv) were obtained on this substance.
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9. This cyclization could also be realized by 1. p-TSA or TFA (catalytic amount)/CH_3OH/room temperature, 2. Δ ($C_6H_5CH_3$-C_2H_5OH/reflux), or 3. hν (360 nm)/I_2/CH_3CN.
10. The spin-spin coupling constant between the 5- and 6-protons could not be determined for 8, because multiple signals corresponding to four protons appeared at the 3.0-3.8 ppm region. Tri-N-methyl derivative was prepared from 8 by treatment with methyl iodide in the presence of silver oxide in DMF at room temperature.
11. J. L. Wong, R. Oesterlin, and H. Rapoport, J. Am. Chem. Soc., 93, 7344 (1971).
12. Higher stereospecificity was observed in a system similar to 7.[13]
13. H. Tanino, T. Nakata, T. Kaneko, and Y. Kishi, a manuscript in preparation.