ran[12] and 6-ethyl-5-methyl-2*H*-pyran-2-one,[13] respectively, and to **6b** which was identified as 3-ethyl-4-methyl-2*H*-pyran-2-one on the basis of its spectroscopic properties.[14]

2-Hydroxypyrylium cations **3a** and **4a** or **3b** and **4b** arising from irradiation of **1a** or **1b** can be adequately rationalized in terms of the mechanism previously suggested by us[1,2] and later by Barltrop and his colleagues,[3,4] which is outlined in Scheme I. Although the mechanistic details for the formation of furyl cations **2a** or **2b** are not clear, it seems likely that they arise from oxobicyclohexenyl cations **9a** or **9b** at the expense of **4a** or **4b.** This suggestion is consistent with the observation that the substituent at C-3 of **1a** or **1b** is found in the side chain of **2a** or **2b.** Failure to observe furyl cations of type **11** may indicate a reluctance of oxobiocyclohexenyl cations of type **10** to undergo this type of isomerization.[15] Alternatively, the known instability of furaldehydes in 96% H_2SO_4, even at 0 °C, may account for their absence.

Recently, Barltrop and his colleagues have shown that in certain cases 2-hydroxypyrylium cations arise via a sulfuric acid adduct, presumably formed by bisulfate anion trapping of a 4-hydroxyoxobicyclohexenyl cation of type **8.**[16] This type of intermediate is formed in particularly high yield and is readily observed upon photolysis of 3,5-dimethyl-4-hydroxypyrylium cation. Although we observe no such intermediates upon photolysis of **1a** or **1b** at room temperature, irradiation of **1a** at 0 °C was accompanied by the appearance of new methyl signals of low intensity in the NMR spectrum at δ 1.8, 1.9, and 2.1 ppm, similar in position to those observed upon photolysis of the 3,5-dimethyl-4-hydroxy cation.[16] Under these conditions, however, whereas the intensity of the NMR signals for furyl cation **2a** were not diminished, the formation of 2-hydroxypyrylium cations **3a** and **4a** was almost completely suppressed. The NMR signals due to these latter cations, however, increased at the expense of the new low intensity methyl signals after the irradiated solution was allowed to warm to room temperature. During these changes, however, no increase in the intensity of the furyl cation signals was observed. These observations indicate that whereas 2-hydroxypyrylium cations **3a** and **4a** may arise from a thermally labile bisulfate adduct, furyl cation **2a** is not formed from such an intermediate.

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(12) Synthesized by treating 2-methylfuran with propanoic anhydride in the presence of phosphoric acid: 100-MHz NMR (CCl_4) δ 1.24 (t, J = 7.5 Hz, 3 H), 2.38 (d, J ~0.6 Hz, 3 H), 2.74 (q, J = 7.5 Hz, 2 H), 6.08 (d of q, J = 3 Hz and ~0.6 Hz, 1 H), 6.96 (d, J = 3 Hz, 1 H); IR (CCl_4) 2980, 2940, 1680, 1205, and 910 cm^{-1}.
(13) 6-Ethyl-5-methyl-2*H*-pyran-2-one was synthesized independently starting with the monocyanoethylation of 3-pentanone. See ref 9: 100-MHz NMR (CCl_4) δ 1.20 (t, J = 7.5 Hz, 3 H), 1.90 (s, 3 H), 2.44 (q, J = 7.5 Hz, 2 H), 5.92 (d, J = 9.6 Hz, 1 H), 6.92 (d, J = 9.6 Hz, 1 H); IR (CCl_4) 2980, 2940, 1735, 1642, and 1300 cm^{-1}.
(14) M^+ (124); IR (CCl_4) 2960, 1720, 1645 cm^{-1}: 100-MHz NMR (CCl_4) δ 1.08 (t, J = 7.5 Hz, 3 H), 2.10 (s, 3 H), 2.46 (q, J = 7.5 Hz, 2 H), 5.84 (d, J = 5.6 Hz, 1 H), 7.18 (d, J = 5.6 Hz, 1 H).
(15) Formation of furyl cations presumably involves ring opening of the oxobicyclohexenyl cation with considerable charge localization on C-6. In **9a** and **9b,** alkyl group substitution at C-6 would serve to stabilize this charge, while in **10a** and **10b,** positive charge would not be similarly stabilized. It also seems plausible that 3-hydroxypyrylium cations are transients in these isomerizations. Ring opening of such intermediates would be subject to identical substituent effects.
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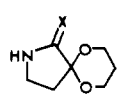
Received October 13, 1976

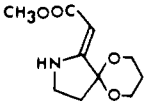
A Stereospecific Total Synthesis of *d,l*-Saxitoxin[1]

Sir:

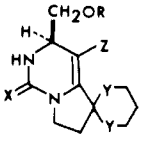
Saxitoxin is the neurotoxin isolated from Alaska butter clams (*Saxidomus giganteus*), toxic mussels (*Mytilus californianus*), and axenic cultures of *Gonyaulax catenella* and is one of the most toxic nonprotein substances known.[2] The structure of saxitoxin was established by x-ray crystallography.[3,4] The toxin was also found in aged extracts of scallops collected during a *Gonyaulax tamarensis* bloom.[2] 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.[5] Two of the three new toxins were shown to be 11α- and 11β-hydroxysaxitoxins (gonyautoxin II and III).[6] In this communication we wish to report the first total synthesis of *d,l*-saxitoxin **13.**

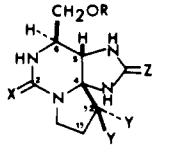


1 : X=O
2 : X=S



3





4 : X=S, Y=O, Z=CO_2CH_3, R=$CH_2C_6H_5$
5 : X=O, Y=O, Z=CO_2CH_3, R=$CH_2C_6H_5$
6 : X=S, Y=O, Z=$NHCONH_2$, R=$CH_2C_6H_5$
7 : X=S, Y=S, Z=$NHCONH_2$, R=$CH_2C_6H_5$

8 : X=S, Z=O, Y=$S(CH_2)_3S$, R=$CH_2C_6H_5$
10 : X=Z=NH, Y=$S(CH_2)_3S$, R=$CH_2C_6H_5$
11 : X=Z=NH, Y=$S(CH_2)_3S$, R=H
12 : X=Z=NH, Y=OH,OH, R=H
13 : Saxitoxin X=Z=NH, Y=OH,OH, R=$CONH_2$

Methyl 2-oxo-4-phthalimidobutyrate[7] was converted to the lactam **1**[8] (mp 104–105 °C) in two steps (1. $HO(CH_2)_3OH/p$-TSA/$C_6H_5CH_3$/reflux, 2. $NH_2NH_2{\cdot}H_2O$/CH_3OH/reflux) in 74% yield. Phosphorus pentasulfide

treatment of **1** in benzene at 80 °C gave thiolactam **2**[8] (mp 151–152 °C), which was converted to the vinylogous carbamate **3**[8] (mp 177–178 °C; λ_{max}^{MeOH} 283 nm (ϵ 19 900); $\delta_{ppm}^{CDCl_3}$ 1.60 (2 H, m), 2.34 (2 H, t, J = 7 Hz), 3.52 (2 H, t, J = 7 Hz), 3.62 (3 H, s), 4.00 (4 H, m), 4.90 (1 H, s), 7.58 (1 H, broad s)) in two steps (1. $CH_3COCHBrCO_2CH_3$/$NaHCO_3$/CH_2Cl_2/reflux,[9] 2. KOH/CH_3OH/50 °C) in 50% overall yield from **1.** The vinylogous carbamate **3** was condensed with benzyloxyacetaldehyde[10] and silicon tetraisothiocyanate[11] in benzene at room temperature, followed by a 110 °C workup in toluene,[12] to yield the thiourea ester **4**[8] (mp 147–148 °C; λ_{max}^{MeOH} 310 nm (ϵ 11 700); $\delta_{ppm}^{CDCl_3}$ 1.40 (2 H, m), 2.33 (2 H, m), 3.47 (2 H, m), 3.75 (3 H, s), 3.95 (6 H, m), 4.40 (1 H, m), 4.50 (2 H, s), 6.87 (1 H, broad s), 7.26 (5 H, s)) in 75% yield. The structure of **4** was concluded from the fact that **4** could be smoothly converted in two steps (1. $Et_3O^+BF_4^-$/$NaHCO_3$/CH_2Cl_2/room temperature, 2. *m*-$ClC_6H_4CO_3H$/wet CH_2Cl_2/0 °C) to the 2-oxo-dihydropyrimidine **5**[8] (mp 134–135 °C; λ_{max}^{MeOH} 293 nm (ϵ 7400)), which was identical with the authentic substance prepared by the isocyanic acid procedure reported previously.[13] The thiourea ester **4** was transformed to the thiourea urea **6**[8] (mp 124–126 °C; λ_{max}^{MeOH} 262 nm (ϵ 8600), 307 (9900); $\delta_{ppm}^{CD_3OD}$ 1.45 (2 H, m), 2.15 (1 H, m), 2.65 (1 H, m), 3.52 (2 H, d, J = 4 Hz), 3.73 (2 H, d, d, J = 9, 6 Hz), 4.00 (4 H, m), 4.54 (2 H, s), 5.02 (1 H, t, J = 4 Hz), 7.26 (5 H, s)) in four steps (1. $NH_2NH_2 \cdot H_2O$/CH_3OH/room temperature, 2. NOCl/CH_2Cl_2/−50 °C, 3. 90 °C/C_6H_6, 4. NH_3/C_6H_6/room temperature) in 75% overall yield.

The cyclization condition previously developed in this laboratory[13] was not suitable for the thiourea urea **6,** since **6** was extremely acid labile. This difficulty was overcome by exchanging the ketal group of **6** with the thioketal group (note acid stability of thioketals). Thus, **6** was converted into the thioketal thiourea **7**[8] (mp 108–111 °C; λ_{max}^{MeOH} 265 nm (ϵ 9200), 301 (8900); $\delta_{ppm}^{CDCl_3}$ 2.00 (2 H, m), 2.80 (6 H, m), 3.57 (2 H, m), 4.01 (2 H, m), 4.54 (2 H, s), 4.75 (2 H, broad s), 4.85 (1 H, m), 6.68 (1 H, broad s), 6.75 (1 H, broad s), 7.28 (5 H, s)) in 63% yield by treatment with 1,3-propanedithiol in acetonitrile in the presence of boron trifluoride etherate at room temperature. The thioketal thiourea **7** was warmed in a mixture of acetic acid and trifluoroacetic acid (v/v = 9/1) at 50 °C for 18 h to yield the tricyclic thiourea **8**[8] (50% yield; mp 158–160 °C; λ_{max}^{MeOH} 255 nm (ϵ 20 400); $\delta_{ppm}^{CD_3OD}$ 1.95 (2 H, m), 2.30–3.10 (6 H, m), 3.40–4.15 (5 H, m), 4.54 (2 H, s), 4.63 (1 H, d, J = 2 Hz), 7.31 (5 H, s)) and its C_6 epimer **9**[8] (10% yield; mp >325 °C; λ_{max}^{MeOH} 255 nm (ϵ 20 300); $\delta_{ppm}^{Me_2SO\text{-}d_6}$ 1.85 (2 H, m), 2.75–3.10 (6 H, m), 3.15–3.95 (6 H, m), 4.47 (2 H, s), 6.92 (1 H, s), 7.30 (5 H, s), 7.70 (1 H, s), 8.04 (1 H, s)).[13,14] In neat trifluoroacetic acid,[13] the ratio of the cyclization products **8** and **9** was 1:5 in favor of **9.** The tricyclic thioureas **8** and **9** were not interconvertible under acetic acid–TFA or –TFA conditions. A possible rationalization for the stereochemistry outcome of this cyclization had been proposed.[13] The stereochemistry assignment of **8** was made by analysis of the NMR spectrum; $J_{5,6}$ was found to be 2.0 Hz for **8,** which is close to that (1.3 Hz) of saxitoxin.[15]

The tricyclic thiourea **8** was converted to the diguanidine **10** in two steps (1. $Et_3O^+BF_4^-$/$NaHCO_3$/CH_2Cl_2/room temperature, 2. $EtCO_2NH_4$/135 °C). The product was isolated as its dipicrate salt[8] (mp 124–126 °C; $\delta_{ppm}^{CD_3OD}$ 2.04 (2 H, m), 2.3–3.2 (6 H, m), 3.63 (5 H, m), 4.51 (2 H, s), 4.95 (1 H, d, J = 1 Hz), 7.25 (5 H, s), 8.71 (4 H, s)) in 33% yield.[16] The hydrochloride salt of **10** was treated with boron trichloride in methylene chloride at 0 °C to yield decarbamoylsaxitoxin thioketal **11,** which was isolated as its hexaacetate[8] (Ac_2O/Py/room temperature) in 75% yield. NBS treatment of the hexaacetate in wet acetonitrile at 15 °C, followed by methanol treatment at 100 °C, gave decarbamoylsaxitoxin **12**[8] dihydrochloride as an amorphous solid (homogeneous on silica gel TLC in different solvents systems[17]) in 30% yield.[18] Decarbamoylsaxitoxin thus synthesized was identical with the authentic decarbamoylsaxitoxin, derived from natural saxitoxin,[17,19] by comparison of the NMR spectrum, silica gel TLC in different solvent systems,[17] and toxicity.

Chlorosulfonyl isocyanate[20] treatment of **12** in formic acid at 5 °C, followed by hot water workup, gave *d,l*-saxitoxin **13**[8] sulfate. The synthetic substance was isolated by workup with a weakly acidic ion exchange resin and then Sephadex LH-20 column chromatography in 50% yield.[18,21] Synthetic saxitoxin was an amorphous solid (homogeneous on silica gel TLC in different solvent systems[2]) and identical with natural saxitoxin[19] by comparison of the NMR spectrum, silica gel TLC, and toxicity.[22]

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

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Stacked Double-Macrocyclic Ligands. 1. Synthesis of a "Crowned" Porphyrin

Sir:

The recognition that a large number of enzymes have two metal ions held in close proximity in their active sites has stimulated considerable interest in the chemistry of binuclear