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SYNTHESIS OF (±)-PROSURUGATOXIN AND RING TRANSFORMATION OF PROSURUGATOXIN INTO SURUGATOXIN

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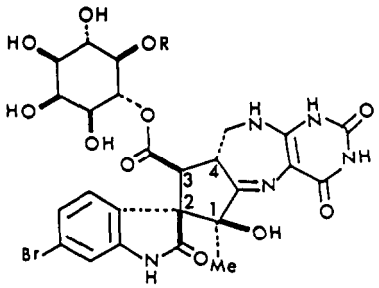
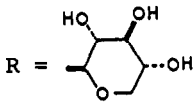
Summary: Synthetic identification of prosurugatoxin and data indicating a possible mechanism for the ring transformation of prosurugatoxin into surugatoxin are presented.

Neosurugatoxin 1,[1] isolated from the toxic Japanese ivory shell, Babylonia japonica, by Kosuge and Tsuji et al. in 1981, is a causative agent of intoxication following ingestion of the toxic shell. This toxin accounts for half the total toxicity of the shell. In 1985, the Kosuge group isolated a new toxic component from the same toxicated shell which accounts for the remaining toxicity of the above shell.[2] From spectral data and the skeletal conversion of this new toxin into a non-toxic compound of surugatoxin 2,[3] its structure was determined to be the de-xylopyranosyl neosurugatoxin shown in structure 3[2] and designated 3 as prosurugatoxin.

The present authors succeeded in synthesizing 3, starting from carboxylic acid 4,[4] the aglycone of both neosurugatoxin 1 and prosurugatoxin 3. This paper provides confirmation of the structure of 3 as prosurugatoxin and presents a possible mechanism for the ring transformation of 3 into surugatoxin 2. Aglycone 4, prepared from 6-bromoisatin and methylthioethyl 4-phthalimidoacetoacetate in 13 steps as reported in our previous paper,[4] was esterified with (±)-2,3-cyclohexylidene-4,5-isopropyridene-1-O-methoxymethyl-myo-inositol[5] (1.2 equiv) in the presence of picryl chloride (step-wise addition, 3.6 equiv) in pyridine at room temperature for 1 hr to give the desired ester 5 as a mixture of diastereoisomers subsequently separated by repeated silica gel TLC [i) MeOH-CH_2Cl_2=1:50, ii) THF-n-hexane=3:8; more polar isomer 5A,[6] 11.6%, less polar isomer 5B,[7] 21.1%]. As in the synthesis of neosurugatoxin,[4] 5A gave natural prosurugatoxin 3 by the following procedure. Hydrolysis of 5A with 0.1N KOH in MeOH under nitrogen atmosphere (rt, 45 min) followed by heating a mixture of the resulting deacetylated products 6 with a large amount of AcONa (20 equiv, 60°C, 30 min) in MeOH gave an equilibrium mixture of four stereoisomeric prosurugatoxin derivatives 6 (6a-d, separated by silica gel TLC: i) MeOH-CH_2Cl_2=1:20, ii) AcOEt-benzene=3:2). Since the NMR spectrum of 6b[8] was consistent with that of the natural form, it was collected by recycling the recovered unnatural three isomers 6a, 6c, and 6d [total yield of 6b for five runs, 70% (corrected)]. Treatment of 6b with 90% TFA (rt, 45 min) provided (±)-3 in 75% yield, whose structure was clearly confirmed by comparing its

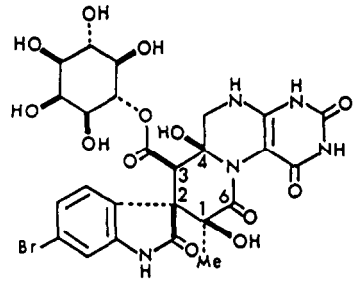


1 : neosurugatoxin

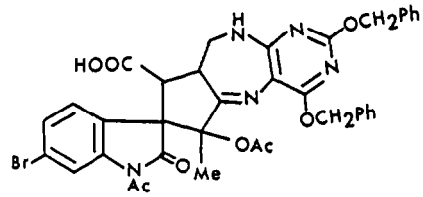


3 : prosurugatoxin

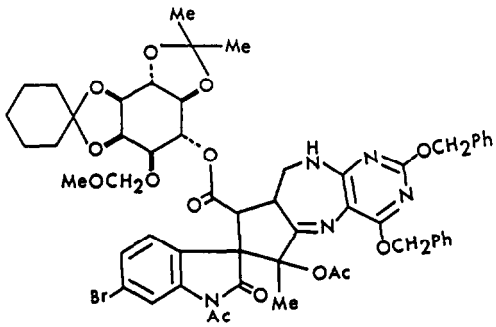
R = H



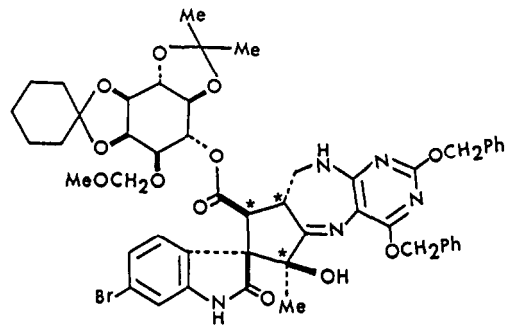
2 : surugatoxin



4

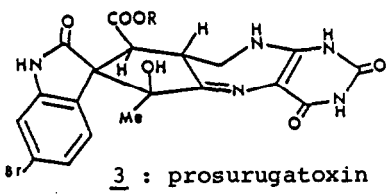


5 (A, B : diastereoisomers)



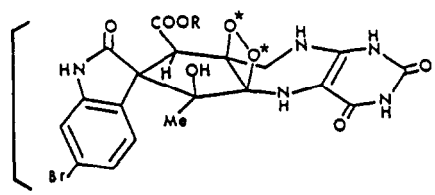
6b (a, c, d : other stereoisomers at C*)

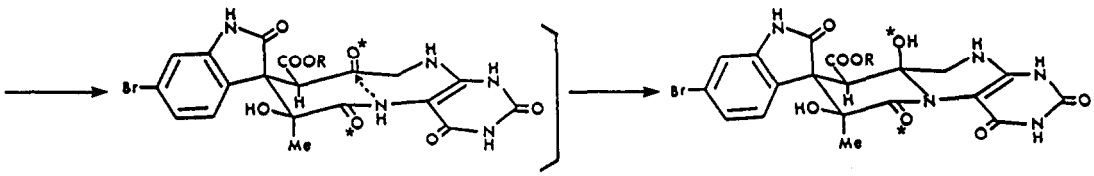
Scheme I



3 : prosurugatoxin

R = 6-myo-inositol





2 : surugatoxin

chromatographical (HPLC: Develosil ODS-5, 30% MeOH in H_2O) and spectral (^{1}H-NMR, SIMS, UV) data with those of natural prosurugatoxin 3.[2)]

The mydriasis activity of synthetic (±)-3 was about half that of natural prosurugatoxin while the activity of the diastereoisomer of (±)-3, prepared from 5B by the same method as for 5A, was essentially the same as that of (±)-prosurugatoxin 3. Thus, mydriasis is not influenced by its stereochemical difference with the myo-inositol ester moiety in 3.

(±)-Prosurugatoxin 3 thus obtained is fairly unstable in DMSO at room temperature for isomerizing a mydriasis active product considered to be the C_1-epimer of (±)-3.[9)] When a solution of prosurugatoxin 3 in 1% acetic acid was kept for a few days at room temperature, an interesting ring transformation occurred, leading to a mydriasis inactive compound identified as surugatoxin 2. An attempt was then made to clarify the mechanism of this novel phenomenon as follows: a solution of (±)-3 (1 mg) in 1% acetic acid (3 ml) was introduced into a cylinder filled with $^{18}O_2$ (100 ml, 1 atom) followed by stirring at room temperature. After two days, the reaction was stopped and the mixture was separated by HPLC (Develosil ODS-5, 30% MeOH in H_2O) into the following three fractions : surugatoxin 2 (40%), C_1-epimer of prosurugatoxin 3 (7%), and prosurugatoxin 3 recovered (45%). Surugatoxin 2 was analyzed by its mass spectrum (SIMS: m/z 690, 688 (MH^+), which clearly indicated the presence of two atoms of ^{18}O in its molecule. The positions of these oxygens should be C_4 and C_6 in 2. Actually, the mass spectrum of the dehydrated derivative, readily available from ^{18}O-labeled 2 with 90% TFA (60°C, 1 hr), indicated the absence of an ^{18}O atom at the C_4-position in 2. Thus, ^{18}O-labelling experiments demonstrate this novel ring transfromation of 3 into 2 to occur stereospecifically via a ten-membered lactam intermediate where it is generated in situ by decomposition of an intermediate dioxetane formed by autoxidation of the imine moiety of 3 (scheme I).

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References and Notes:

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T. Kosuge, K. Tsuji, and K. Hirai, Chem. Pharm. Bull., 30, 3255 (1982).
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3) T. Kosuge, H. Zenda, A. Ochiai, N. Masaki, M. Noguchi, S. Kimura, and H. Narita, Tetrahedron Lett., 2545 (1972).

4) S. Inoue, K. Okada, H. Tanino, and H. Kakoi, Tetrahedron Lett., 27, 5225 (1986).

5) S. Inoue, K. Okada, H. Tanino, K. Hashizume, and H. Kakoi, Tetrahedron Lett., 25, 4407 (1984) and references cited therein.

6) PMR (400 MHz, $CDCl_3$) δ: 1.32(3H, s), 1.36(3H, s), 1.53(3H, s),1.20-1.74(10H, m), 2.02(3H, s), 2.62(3H, s), 2.87(1H, dd, J=10.7, 7.8 Hz), 3.33(3H, s), 3.47(1H, dd, J=3.7, 2.4 Hz), 3.49(1H, ddd, J=12.0, 7.8, 1.5 Hz), 3.68(1H, ddd, J=11.0, 7.8, 2.9 Hz), 3.73(1H, dd, J=7.3, 3.7 Hz), 3.84(1H, d, J=11.0 Hz), 4.01(1H, ddd, J=12.0, 7.3, 2.9 Hz), 4.03(1H, dd, J=10.7, 7.3 Hz), 4.16(1H, t, J=7.3 Hz), 4.57 and 4.65(2H, d of AB, J=6.6 Hz), 4.95(1H, dd, J=7.8, 2.4 Hz), 5.35(2H, s), 5.41 and 5.49(2H, d of AB, J=13.2 Hz), 5.80(1H, br dd, J=7.3, 1.5 Hz), 6.99(1H, d, J=8.1 Hz), 7.24-7.50(11H, m), 8.52(1H, d, J=2.0 Hz).

7) PMR (400 MHz, $CDCl_3$) δ: 1.36(3H, s), 1.38(3H, s), 1.51(3H, s), 1.50-1.72(10H, m), 2.01(3H, s), 2.60(3H, s), 2.88(1H, dd, J=10.6, 8.4 Hz), 3.36 (3H, s), 3.46(1H, t, J=3.0 Hz), 3.51(1H, ddd, J=12.1, 7.7, 1.5 Hz), 3.65(1H, ddd, J=10.6, 7.7, 2.8 Hz), 3.77(1H, dd, J=7.0, 3.0 Hz), 3.81(1H, d, J=10.6 Hz), 4.03(1H, dd, J=10.6, 7.0 Hz), 4.05(1H, ddd, J=12.1, 7.3, 2.8 Hz), 4.17(1H, t, J=7.0 Hz), 4.60 and 4.68(2H, d of AB, J=6.6 Hz), 4.97(1H, dd, J=8.4, 3.0 Hz), 5.35(2H, s), 5.40 and 5.49(2H, d of AB, J=13.2 Hz), 5.82(1H, br dd, J=7.3, 1.5 Hz), 6.96(1H, d, J=8.1 Hz), 7.22-7.48(11H, m), 8.52(1H, d, J=1.8 Hz).

8) PMR (400 MHz, $CDCl_3$) δ: 1.33(3H, s), 1.36(3H, s), 1.41(3H, s), 1.50-1.80(10H, m), 2.93(1H, dd, J=10.6, 8.1 Hz), 3.03(1H, d, J=10.3 Hz), 3.26(1H, ddd, J=12.1, 9.5, 1.0 Hz), 3.36(3H, s), 3.46(1H, dd, J=3.7, 2.6 Hz), 3.79(1H, dd, J=7.3, 3.7 Hz), 3.89(2H, m), 4.02(1H, dd, J=10.6, 7.3 Hz), 4.17(1H, t, J=7.3 Hz), 4.24(1H, br s), 4.63 and 4.67(2H, d of AB, J=6.6 Hz), 5.04(1H, dd, J=8.1, 2.6 Hz), 5.33(2H, s), 5.40 and 5.44(2H, d of AB, J=12.5 Hz), 5.90(1H, br dd, J=6.6, 1.0 Hz), 7.05(1H, d, J=1.8 Hz), 7.06(1H, d, J=8.1 Hz), 7.20(1H, dd, J=8.1, 1.8 Hz), 7.24-7.48(10H, m), 8.17(1H, s).

9) PMR (300 MHz, D_2O, DOH=4.65 ppm) δ: 1.09(3H,s), 2.93(1H, t, J=9.6 Hz), 3.26(1H, dd, J=9.6, 3.1 Hz), 3.25-3.35(2H, m), 3.46(1H, t, J=9.6 Hz), 3.40-3.53(1H, m), 3.79(1H, d, J=10.5 Hz), 3.85(1H, t, J=3.1 Hz), 3.93(1H, dd, J=13.1, 2.6 Hz), 4.81(1H, t, J=9.6 Hz), 7.17(1H, d, J=1.8 Hz), 7.22(1H, dd, J=8.1, 1.8 Hz), 7.27(1H, d, J=8.1 Hz).

The structural proof and the biological properties of this compound will be reported elsewhere.

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