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MODEL EXPERIMENTS ON SURUGATOXIN SYNTHESIS. AN APPROACH IN THE CONSTRUCTION OF THE PENTACYCLIC RING SYSTEM

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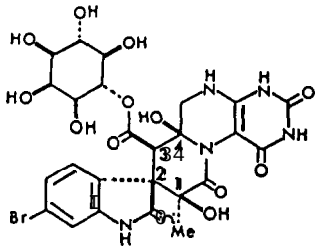
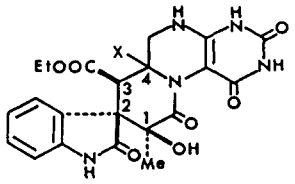
Summary: Synthesis of the ethyl ester 2a of the debromo-aglycone of surugatoxin 1 has been achieved in 10 steps starting from readily available ethyl 2-(2-oxo-3-indolenyl)-3-oxo-4-phthalimidobutyrate 3.

Surugatoxin 1, isolated from the toxic ivory shell (Babylonia japonica) by Kosuge et al.[1] in 1972, is a fascinating marine natural product. The unique structure of this compound is characterized by a highly functionalized spiro-oxindole moiety, involving a consecutive four asymmetric carbons, which is fused to a tetrahydropteridine ring. To establish a method for the construction of this interesting new ring system, we first studied the synthesis of the ethyl ester 2a of the debromo-aglycone of surugatoxin 1 as a model compound.

Ethyl 2-(2-oxo-3-indolenyl)-3-oxo-4-phthalimidobutyrate 3 (mp 245-250°C (decomp)), a starting material for the proposed model study, was readily available from isatin and ethyl 4-phthalimidoacetoacetate[2] under a Knoevenagel condition (79%, AcOH-piperidine (7:1), dry benzene, reflux, 5 h). Reduction of 3 with $Na_2S_2O_4$ in boiling EtOH gave an enolized diastereomeric mixture of 4 (90%, mp 183-184°C). Treatment of 4 with $NH_2NH_2 \cdot H_2O$ (2.5 equiv, 0°C, 20 min) in CH_2Cl_2-MeOH (4:1) followed by hydrolysis (10% HCl) gave the unstable amino-ketone which was isolated as its hydrochloride 5 (70% overall yield). Coupling of 5 with 2,6-dibenzyloxy-4-ethylsulfonyl-5-nitropyrimidine[3] in dioxane-H_2O in the presence of an excess amount of $NaHCO_3$ at room temperature

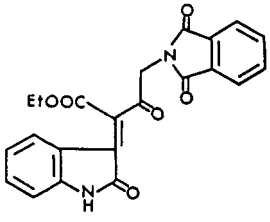


1 surugatoxin



2a X = β-OH

2b X = α-OH



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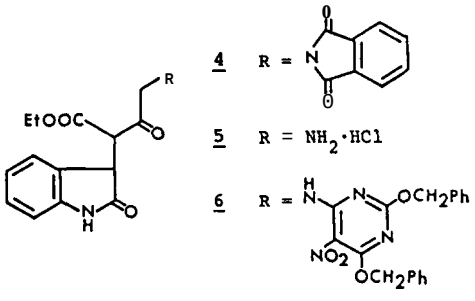
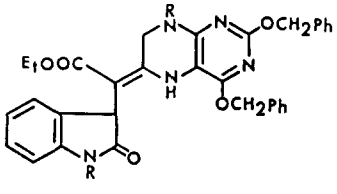


4 R =

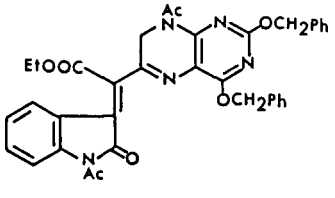
5 R = $NH_2 \cdot HCl$

6 R =



7 R = H

8 R = AC



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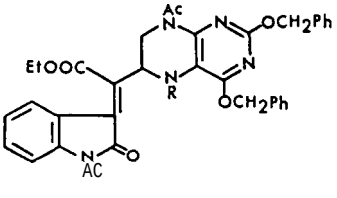
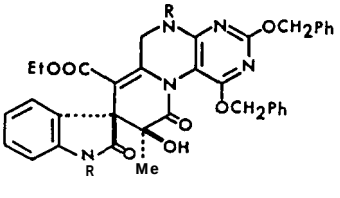


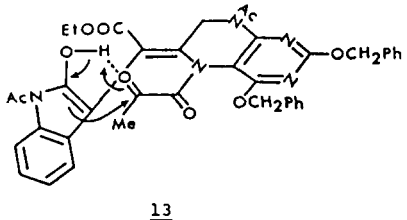
10 R = H

11 R = COCOMe



12 R = Ac

14 R = H



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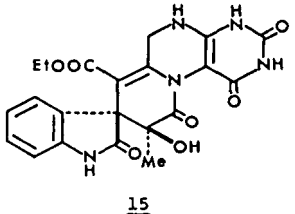

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for 7 h yielded a mixture of inseparable diastereoisomers 6 (92%, mp 192-193°C (decomp)), which was reduced (Zn/2N HCl-THF) to give the corresponding tetrahydropteridine derivative 7[4] as a single product in quantitative yield. When 7 was acetylated with Ac_2O-pyridine (10:3, 80°C, 2 h), 1,4-dehydrogenation occurred simultaneously to give the dihydropteridine diacetate 9[5] (2:1 E, Z mixture, 50% combined yield) together with 8.[6] Selective reduction of the imine moiety in 9 with $NaBH_3CN$ (6 equiv)-2N HCl (6 equiv) in EtOAc gave the sec-amine 10 (E, Z mixture, 90% combined yield). Then, it was treated with pyruvoyl chloride (18 equiv) in dry benzene under cooling to afford the amide 11[7] as a 2:1 E, Z mixture in a combined yield of 80%. Ring closure of 11, probably via 13, was effected when a solution of 11 in pyridine was heated at 50°C for 3 h under a nitrogen atomosphere. An oily residue obtained after extractive workup was purified by silica gel chromatography (5% MeOH-CH_2Cl_2), affording the desired key intermediate 12 (75%, mp 206-207°C) as a single product, whose structure was verified via ^{1}H-NMR analysis.[8] Alkaline hydrolysis of 12 with MeONa-MeOH (2 equiv) in CH_2Cl_2 at 0°C for 30 min furnished 14 (mp 240-241°C) in 83% yield. Debenzylation of 14 (90% TFA, room temperature, 40 min) led to the dehydrated surugatoxin derivative 15[9] in nearly quantitative yield. Heating 15 (or 14) in 90% TFA at 60°C for 6 h resulted in the formation of an equilibrium mixture which was separated by chromatography (silica gel TLC : EtOAc-MeOH-acetone-H_2O=6:2:2:1) to give the surugatoxin derivative 2a (30%) together with another stereoisomer 2b (3%)[10] and 15 (50%). Stereochemical assignments of 2a and 2b were made via comparison of ^{1}H- and ^{13}C-NMR spectra to those of other related stereoisomers and natural surugatoxin 1.[10] Since the chemical shifts of the C_1-methyl of 2a were very close to those of surugatoxin, the stereochemistry of 2a was unequivocally attributable to the natural form. Although the equilibrium was unfavorable for the natural isomer 2a, the yield of which was raised up to 65% by recycling the recovered dehydrated derivative 15 together with 2a. Thus, synthesis of the debromo-aglycone of surugatoxin derivative 2a was completed and we concluded that the method described above would be applicable in the synthesis of natural surugatoxin 1.

REFERENCES AND NOTES

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K. Yamaguchi, T. Okamoto, and Y. Iitaka, Tetrahedron Lett., 22, 3417 (1981).
c: T. Kosuge, K. Tsuji, and K. Hirai, Chem. Pharm. Bull., 30, 3255 (1982).

2) J. K. Mehrotra and S. D. Verma, J. Indian Chem. Soc., 38, 785 (1961).

3) This material was prepared from the known 4-chloro-5-nitrouracil [R. M. Cresswell and H. C. S. Wood, J. Chem. Soc., 4768 (1960)] by the following 4 steps: 1) EtSNa, 2) $POCl_3$, 3) $PhCH_2ONa$, 4) mCPBA.

4) ^{1}H-NMR(DMSO-d_6): δ 4.29 (1H, s), 4.52 (2H, s).

5) Assignment of E, Z stereochemistry of each isomer has remained unknown. Since each isomer yielded the same final product 12, we used the mixture for the subsequent 3 steps without separation.

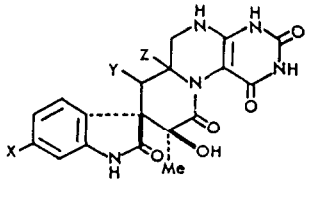
6) This material was readily converted to 9 in high yield by repeated treatment in pyridine-Ac_2O under the same condition.

7) ^{1}H-NMR($CDCl_3$): major isomer, δ 2.04 (3H, s), 2.53 (3H, s), 2.66 (3H, s), 3.67 (1H, dd, J=14, 9 Hz), 5.05 (1H, dd, J=14, 7 Hz), 6.04 (1H, dd, J=9, 7 Hz); minor isomer, δ 2.07 (3H, s), 2.54 (3H, s), 2.74 (3H, s), 3.61 (1H, dd, J=14, 9 Hz), 5.09 (1H, dd, J=14, 7 Hz), 6.80 (1H, dd, J=9, 7 Hz).

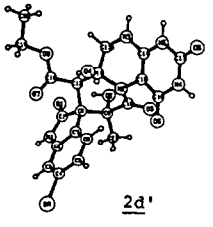
8) ^{1}H-NMR($CDCl_3$): δ 1.35 (3H, S), 2.48 (3H, s), 2.55 (3H, s), 3.45 (1H, br.d, J=16 Hz), 6.30 (1H, br.d, J=16 Hz). Anti-orientation between C_1-methyl and the carbonyl in the oxindole moiety was revealed by the unusually higher chemical shift of the methyl at δ 1.35, requiring a shielding effect of the oxindole ring.

9) ^{1}H-NMR(DMSO-d_6): δ 1.45 (3H, s), 3.80 (1H, d, J=15 Hz), 4.55 (1H, br.d, J=15 Hz).

10) The other stereoisomers 2c and 2d were prepared from 12 by the following 4 steps: 1) MeONa-MeOH, THF, 2) OsO_4, THF, 3) excess BH_3-pyridine complex, AcOH, 4) 90% TFA. The bromo-derivative 2d' was prepared from 6-bromo-isatin in the same way as in the case of 2d. The structure of 2d' was determined by X-ray analysis. The crystals were monoclinic, space group $P2_1/a$, with a=8.551 (2), b=16.523 (2), c=17.820 (2) Å, β=103.71 (1)°, and d(calcd)=1.640 g cm^{-3} for Z=4 ($C_{21}H_{20}BrN_5O_8 \cdot 3H_2O$, MW=604.37).



	X	Y	Z
2a	H,	β-COOEt,	β-OH
2b	H,	β-COOEt,	α-OH
2c	H,	α-COOEt,	β-OH
2d	H,	α-COOEt,	α-OH
2d'	Br,	α-COOEt,	α-OH



2d'

Chemical shifts of the C_1-methyl groups (δ in DMSO-d_6) are shown in the following table:

	surugatoxin 1	2a	2b	2c	2d
^{1}H-NMR	1.34	1.38	1.57	0.75	0.87
^{13}C-NMR	24.423	24.337	24.746	18.720	19.188

Treatment of 2b, 2c, and 2d with 90% TFA (60°C, 6 h) resulted in the same equilibrium mixture as that of 2a.

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