Tetrahedron Letters No. 6, pp 539 - 542, 1978. Pergamon Press. Printed in Great Britain.

THE STEREOSPECIFIC SYNTHESIS OF TETRAHYDROAUSTAMIDE

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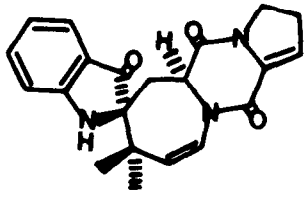
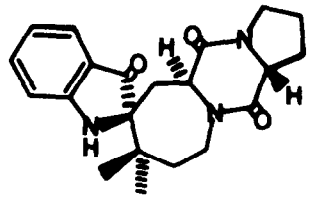
(Received in USA 17 November 1977; received in UK for publication 16 December 1977)

As part of investigations directed toward the total synthesis of austamide (1)[1], a toxic metabolite of *Aspergillus ustus*, we have had the opportunity to study the stereochemical outcome of the oxidation and rearrangement of the indole 5b to *trans*-tetrahydroaustamide (2). A similar process may be involved in the biosynthesis of austamide.[2]

The reduction of 3,3-dimethyl-4-pentynoic acid[3] by lithium aluminum hydride in ether afforded the corresponding alcohol which was reacted with benzyl bromide and sodium hydride in tetrahydrofuran. In this manner 3,3-dimethyl-5-benzyloxy-1-pentyne[4] was obtained in an overall yield of 54%. This acetylene was coupled[5] with *o*-iodoaniline in dimethylformamide in the presence of cuprous iodide and triethylamine at 145° to give the indole 3a (mp 82-83°)[6] as the sole product in 68% yield. The indole 3a was converted to the corresponding gramine 3b (mp 52-53°)[7] in 81% yield which in turn was condensed with diethyl N-benzyloxycarbonyl-L-prolylaminomalonate[8] in the presence of powdered sodium hydroxide which afforded the amidomalonate derivative 3c[4] in 59% yield. Hydrogenolysis of the carbobenzyloxy group in 3c proceeded selectively in methanol and no cleavage of the benzyl ether was observed. The crude amino ester was cyclized in refluxing xylene to a 7:1 mixture of diastereomers in an overall yield of 91% with 4a (mp 162-163°)[9] as the major stereoisomer.[10] The benzyl ether was removed by hydrogenolysis in 1:1 methanol-acetic acid and the resulting alcohol 4b[4] was converted to the mesylate 4c (mp 115-116°)[11] in an overall yield of 85%. This mesylate could in principle cyclize on either the indole nitrogen or the diketopiperazine nitrogen. Experimentally it was found that either mode of reaction could be made to predominate by the appropriate choice of reaction conditions. Reaction with $KOBu^t$ in tetrahydrofuran gave cyclization on the indole nitrogen exclusively. However cyclization under heterogenous conditions (NaH/benzene) gave 5a



1



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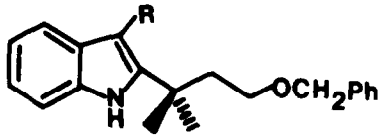
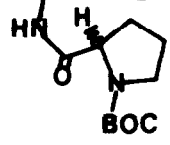
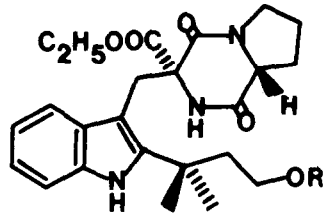


3a R = H

3b R = $CH_2N(CH_3)_2$

3c R = $CH_2C(CO_2C_2H_5)_2$

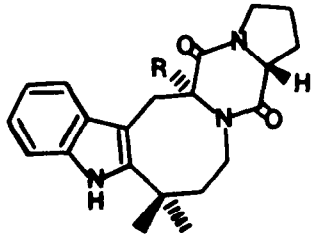




4a R = CH_2Ph

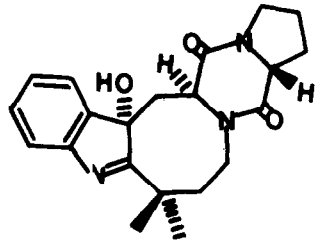
4b R = H

4c R = SO_2CH_3



5a R = $CO_2C_2H_5$

5b R = H



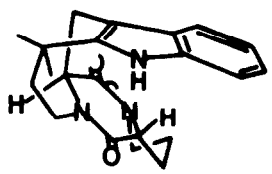
6

(mp 201-202°)[12] as the major product in 65% yield. Hydrolysis and decarboxylation proceeded smoothly and stereospecifically and afforded the *trans* diketopiperazine 5b (mp 285-286°)[13,14] in 76% yield as the only stereoisomer detected.

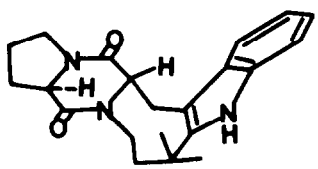
Whereas oxidation of 5b under a variety of conditions [O_2/Pt/EtOAc[15]; $Pb(OAc)_4/CH_2Cl_2$[16]; $O_2/(C_6H_5CO_2)_2/CHCl_3$[17]; $(C_6H_5COO)_2$/dioxane[18]] was unsuccessful, we were delighted to find that 5b was converted to the corresponding hydroxy indoline 6[4] by treatment with 1 equiv. of *m*-chloroperbenzoic acid in methylene chloride at room temperature. The gross structure of 6 was

confirmed by reduction with sodium borohydride followed by treatment with 3N hydrochloric acid which gave the indole 5b as expected.[15] Rearrangement of 6 under acidic conditions (3N HCl/EtOH/reflux) afforded *trans*-tetrahydroaustamide 2 (mp 228-231°) as the only stereoisomer detected in an overall 40% yield from 5b. It was identical in all respects (NMR, UV, MS, TLC) with an authentic sample of *trans*-tetrahydroaustamide.[1,19]

A possible explanation of this remarkable stereospecificity is as follows. Examination of the Dreiding Models reveals that among the many conformations available to the eight-membered ring in 5b, the folded conformation A and the extended conformation B appear to be the most stable. Since the pinacol rearrangement of 6 to 2 must proceed stereospecifically, the overall stereochemistry in the conversion of 5b to 2 is governed by the stereochemistry of the oxidation. Thus the experimental results imply that attack of the oxidizing agent must occur exclusively from the β side of the indole to give 6 with the stereochemistry as shown. We therefore suggest that the folded conformation predominates in this system and hence the oxidation is extremely stereospecific, the α side of the indole being effectively blocked by the eight-membered ring. This would clearly not be the case if the extended conformation predominated; in that event the α side of the indole is less hindered and attack of the oxidizing agent would occur preferentially from the α side.



A



B

Since examination of the Dreiding Models indicates that the preferred conformation of the presumed biogenetic precursor[2] of austamide should be similar to that of the indole 5b, we plan to extend this stereospecific oxidation and rearrangement to the total synthesis of austamide itself.

Acknowledgment We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We are indebted to Dr. P. S. Steyn for a sample gift of austamide and tetrahydroaustamides.

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1. P. S. Steyn, Tetrahedron, 29, 107 (1973); J. Coetzer and P. S. Steyn, Acta Cryst., B29, 685 (1973).

2. See, for example, P. G. Sammes, "Naturally Occurring 2,5-Dioxopiperazine and Related Compounds", Fortsch. Chem. org. Naturstoffe, 32, 51 (1975).

3. O. L. Behrens, J. Corse, D. E. Huff, Q. F. Soper, and C. W. Whitehead, J. Biol. Chem., 175, 771.

4. Satisfactory spectroscopic data were obtained for this substance.

5. C. E. Castro, E. J. Gaughn, and D. C. Owsley, J. Org. Chem., 31, 4071 (1966).

6. NMR ($CDCl_3$, δ) 1.39 (6H, s); UV (CH_3OH, λ_{max}) 289nm (log ε 3.85), 218 (4.71); MS (m/e) 293 (M^+, 25%), 159 (100), 158 (67).

7. NMR ($CDCl_3$, δ) 1.51 (6H, s), 2.20 (6H, 2); MS (m/e) 351 (M^+, 11%), 306 (15), 145 (100).

8. R. Ritchie and J. E. Saxton, J. C. S. Chem. Comm., 612 (1976).

9. NMR ($CDCl_3$, δ) 1.35 (3H, t, J=7Hz), 1.48 (3H, s), 1.50 (3H, s); MS (m/e) 531 (M^+, 1%), 306 (52), 144 (100).

10. *Trans* configuration was assigned to this substance, based on the chemical shift of the methine proton of the proline moiety. The chemical shift of this proton is 3.10 ppm for the major isomer and 4.00 ppm for the minor isomer.

11. NMR ($CDCl_3$, δ) 1.35 (3H, t, J=7Hz), 1.53 (6H, s), 2.78 (3H, s); MS (m/e) 529 (M^+, 1%), 433 (5), 198 (100).

12. NMR ($CDCl_3$ δ) 1.30 (3H, t, J=8Hz), 1.50 (3H, s), 1.65 (3H, s); MS (m/e) 423 (M^+, 100%), 250 (99).

13. NMR ($CDCl_3$ δ) 1.35 (3H, s), 1.58 (3H, s); MS (m/e) 351 (M^+, 100%), 198 (63).

14. Based on the NMR spectrum, the *trans* configuration was tentatively assigned to this substance, which was confirmed by the successful transformation of 5b into *trans*-tetrahydroaustamide.

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16. N. Finch, C. W. Gemerden, I. H. C. Hsu, and W. I. Taylor, J. Am. Chem. Soc., 85, 1520 (1963).

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18. S. Nakatsuka, T. Fukuyama, and Y. Kishi, Tetrahedron Lett., 1549 (1974).

19. Although we started the synthesis with L-proline, the synthetic tetrahydroaustamide was found to be racemic. Racemization of the proline residue seems to have taken place primarily at the transformation of 4c to 5a.