Tetrahedron Letters,Vol.24,No.48,pp 5339-5342,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain ©1983 Pergamon Press Ltd.

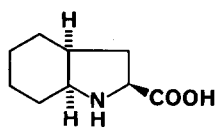
DIASTEREOSELECTIVE SYNTHESIS OF BICYCLIC AMINO ACIDS VIA RING CONTRACTION OF α-CHLOROLACTAMS

R. Henning + and H. Urbach

Hoechst AG, Pharma Synthese, 6230 Frankfurt/Main 80

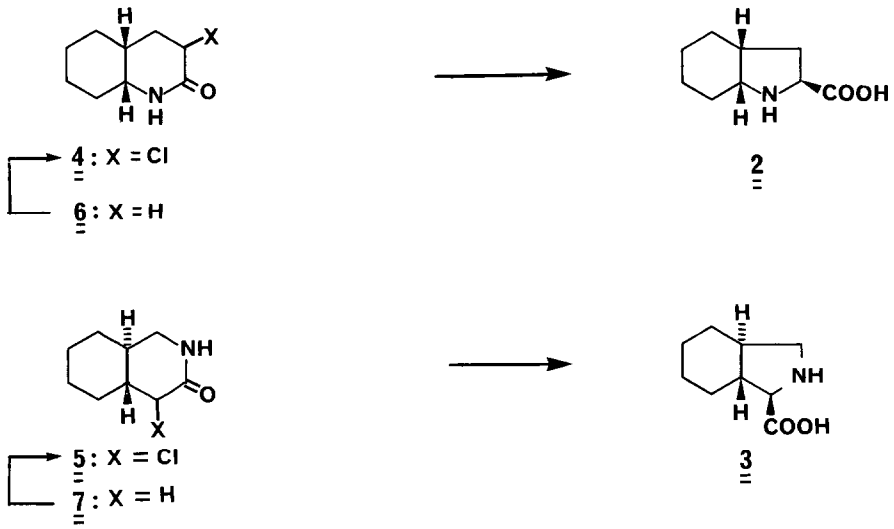
Summary: Bicyclic lactams were converted to their α-chloro-derivatives and subjected to ring contraction under basic conditions to give bicyclic acids in diastereoselective fashion.

In the process of our program directed toward the synthesis of angiotensin converting enzyme inhibitors we were faced with the need to prepare a variety of amino acids containing a proline moiety.
The formal annulation of alicyclic rings to the basic proline system creates new centers of asymmetry; there is little literature precedent for stereoselective approaches leading to these derivatives [1]. Groups at Warner-Lambert Comp. and Schering Corp. have described the synthesis of octahydroindole-2-carboxylic acid by hydrogenation of the corresponding aromatic compound, which produces the S,S,S-isomer 1 after separation of enantiomers[2]. We describe here our efforts to synthesize compound 2 which is the 2-exo isomer of 1, and the related trans-isoindole derivative 3 in diastereoselective fashion.



1

We used as a key reaction the base promoted Favorskii type ring contraction of α-chlorinated lactams 4 (mp. 185°C, NMR (60 MHz, $CDCl_3$): δ = 7.8 (br. s, 1H); 4.50 (m,1H); 3.25 (m,1H); 2.13 (d,2H); 1.8-1.1(m,9H)ppm) and 5 (NMR (60 MHz, $CDCl_3$): δ = 7.0 (br. s,1H); 4.0 (d,J = 10 Hz, 1H); 3.2 - 3.0 (m,2H); 2.5-1.0 (m,10H)ppm), which were prepared from the known lactams 6 [3] and 7 [4] by a dichlorination/monodechlorination sequence (PCl_5/SO_2Cl_2,$CHCl_3$, reflux; then H_2/Raney-Ni, ethanol, NEt_3) [5] in 38 % and 53 % yield, respectively.



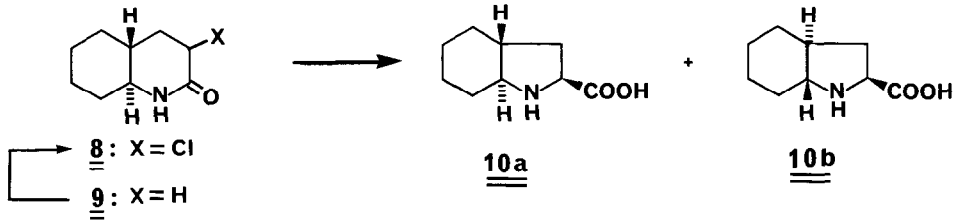
This type of reaction has been used previously for construction of substituted prolines [6] and large ring analogues of proline [7], but the stereochemical outcome in cases, where isomers are possible, has not been specified. Several basic reagents are suitable for effecting the rearrangement [6,7], the best in our hands being barium hydroxide in aqueous solution.

Thus, 4 and 5 were refluxed with $Ba(OH)_2 \cdot 8\ H_2O$ (1.05 equiv.) for 2 hrs, the solution neutralized with 2 N sulfuric acid or carbon dioxide, which precipitates all inorganic material, filtered and the solution evaporated to dryness to give 2 (amorphous solid, mp. 115°C (dec.)) in 94 % yield and 3 (mp. 246°C, R_f = 0.46, CH_2Cl_2/MeOH/HOAc/H_2O = 10 : 5 : 1 : 1) in 96 % yield. In this way 2 was obtained admixed with 1 (ratio 9 : 1), whereas 3 was obtained in isomerically pure form, according to the 270 MHz NMR spectra of their benzyl esters [8]. The exo position of the carboxyl group in 2 has been proven by comparison with an authentic sample of its benzyl ester, which has been obtained by an independent route [9].

The high diastereoselectivity in these two cases probably reflects the thermodynamic equilibrium between the respective isomers, which can be established easily under the strongly basic reaction conditions. In 1, there is a 1,3-cis interaction between the carboxyl group and the six-membered ring, which makes this isomer less stable compared with 2. This situation becomes even more severe in the case of 3, where we would have a 1,2-cis interaction in the other isomer and which is, as a consequence, not present to any sizable extent in the equilibrium mixture.

This assumption is underlined by the results obtained with trans-chlorolactam 8 (mp. 115-120°C) obtained from trans-lactam 9 [13]. We obtained under the described reaction conditions a 1 : 1 mixture of amino acids 10a and 10b (mp. 274 - 276°C).

The ratio was deduced from the NMR spectrum of the benzyl ester mixture [14].



Since the bicyclic skeleton is practically flat in the trans-case, due to the absence of strain there should be not much difference in energy between 10a and 10b, which is expressed by their equal distribution under equilibrating conditions. The preparation of angiotensin converting enzyme inhibitors from the above amino acids and their pharmacological properties will be presented in a future paper.

Acknowledgement: We are grateful to Dr. H.-W. Fehlhaber for analyticalsupport.

References and Notes

1) A review on the synthesis of proline derivatives has been published; A.B. Mauger and B. Witkop, Chem. Rev., 65, 47 (1965); for further examples see the following paper in this issue: R. Henning and H. Urbach, Tetrahedron Lett., (1983)

2) M. L. Hoefle and G. Bobowski, Europ. Pat. Appl., 37 231 (1982); B. R. Neustadt, E. H. Gold and E. M. Smith, Europ. Pat. Appl.,50 800 (1982).

3) T. Ibuka, N. Masaki, I. Saji, K. Tanaka and Y. Inubushi, Chem. Pharm. Bull., 23, 2779 (1975); T. Momose, T. Miyata and T. Imanishi, Heterocycles,9, 17 (1978).

4) R. A. Abramovitch and J. M. Muchowski, Can. J. Chem., 38, 557 (1960).

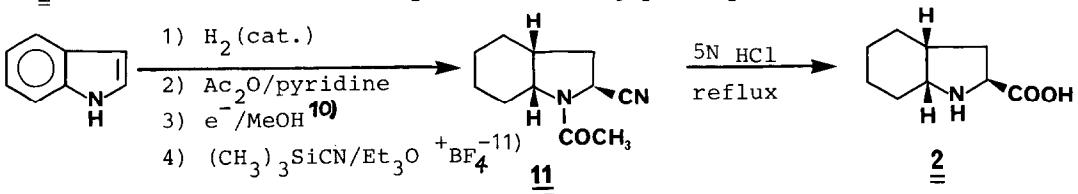
5) W. C. Francis, J.R. Thornton, J. C. Werner and T. R. Hopkins, J. Amer. Chem. Soc.,80, 6238 (1958); R. J. Wineman, E.-P. Hsu and C. E. Anagnostopoulos, ibid., 80, 6233 (1958).

6) G.B.R. de Graaf, W. Ch. Melger and G. Van de Kolk, Rec. Trav. Chim., 81, 786 (1962); K. Kariyone, Chem. Pharm. Bull., 8, 1110 (1960); T. Takahashi and K. Kariyone, Yakugaku Zasshi, 79, 711 (1959), Chem. Abstr., 53, 21940 (1959).

7) H. T. Nagasawa, J. A. Elberling, P. S. Fraser and N. S. Mizuno, J. Med. Chem., 14, 501 (1971); J. A. Elberling and H. T. Nagasawa, J. Heterocycl. Chem., 9, 411 (1972).

8) The benzyl esters were prepared by conventional methods [12]. The following characteristic absorptions were observed: 2-OBzl: δ = 3.95 (t,J=8Hz); 3.29 (q,J=4Hz); 1-OBzl:δ=3.82(dd,J_1=10Hz, J_2=4Hz); 3.08 (q,J=4.8Hz); 3-OBzl:δ=4.0(d,J=10Hz)ppm.

9) 2 has also been obtained by the following pathway:



11 2

H. Urbach, R. Henning, M. Mitzlaff, Tetrahedron Lett., (1983), in preparation.

The relative stereochemistry of 11 has been proven by X-ray crystallography: H. Urbach, R. Henning, M. Mitzlaff ans E. F. Paulus, Tetrahedron Lett., (1983), in preparation.

10) M. Mitzlaff, K. Warning and H. Jensen, Liebigs Ann. Chem., 1713 (1978).

11) V. Asher, C. Becu, M. J. O. Anteunis and R. Calleus, Tetrahedron Lett., 141 (1981).

12) Houben-Weyl-Müller, Methoden der Organischen Chemie, Vol. 15/1, p. 348 ff., Stuttgart 1974.

13) D. Tourwé and G. Van Binst, Bull. Soc. Chim. Belg., 85, 11 (1976).

14) The mixture of benzyl esters shows two triplets at δ = 3.90 and 3.86 ppm of about equal intensity in the 270 MHz ^{1}H NMR spectrum of the free base ($CDCl_3$) and two triplets at δ = 4.49 and 4.46 ppm for the hydrochloride in DMSO-d_6.

(Received in Germany 12 August 1983)