Tetrahedron Letters No.44, pp. 5393-5399, 1966. Pergamon Press Ltd.
Printed in Great Britain.

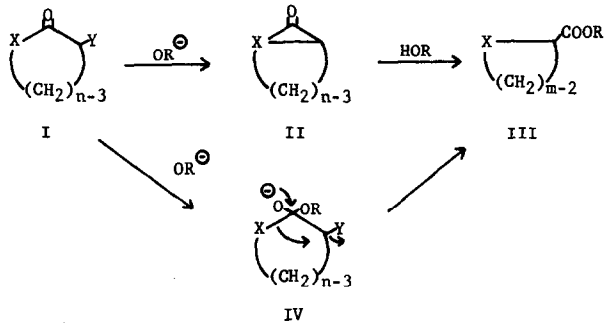
SYNTHESIS OF RING HOMOLOGS OF PROLINE BY THE FAVORSKII REARRANGEMENT OF α-HALOLACTAMS

H. T. Nagasawa and J. A. Elberling

Laboratory for Cancer Research, Minneapolis Veterans Hospital
and the Dept. of Pharmaceutical Chemistry, University of Minnesota
Minneapolis, Minnesota 55417, U.S.A.

(Received 22 March 1966; in revised form 4 August 1966)

The Favorskii rearrangement (1) of α-halocycloalkanones Ia leads to ring contracted cycloalkanecarboxylic acids or esters IIIa. The reaction is believed to proceed via cyclopropanone intermediates of type IIa, or by way of delocalized intermediates (2). Alternatively, a semibenzilic mechanism (Ia → IVa → IIIa) may be considered; indeed, the latter mechanism must be operative in the rearrangement of 2-bromocyclobutanone (Ib) to cyclopropanecarboxylic acid (IIIb), since D_2O in the reaction medium did not label the ring of isolated IIIb (3).



a: X = CH_2; Y = Cl, Br; R = H, Alkyl

b: X = CH_2; Y = Br; R = H; n = 4; m = 3

c: X = NH; Y = Cl, Br; R = H, Alkyl

Substitution of NH for CH_2 in the position α to the carbonyl group not bearing the halogen substituent in I would give α-halogenated-ω-amino lactams (Ic), which, under Favorskii conditions, might be expected to rearrange to cyclic α-imino acid derivatives IIIc, possibly via the bicyclic aziridinones IIc (X = N). We wish to report that α-halolactams of medium ring size (Ic, n = 8, 9, 10, 11, 12) do indeed rearrange to α-imino acids in good to fair yields on treatment with base, and this rearrangement affords a novel synthesis of the heretofore unknown 7-, 8-, 9-, 10- and 11-membered cyclic α-imino acids homologous to proline, i.e., hexahydroazepine-2-carboxylic acid (IIId), octahydroazocine-2-carboxylic acid (IIIe), octahydroazonine-2-carboxylic acid (IIIf), decahydroazecine-2-carboxylic acid (IIIg), and azacycloundecane-2-carboxylic acid (IIIh), respectively (Table I).*

The reagent of choice for this rearrangement is potassium t-butoxide (in t-butyl alcohol, tetrahydrofuran or dioxan), although even NaOH in aqueous dioxan give rearranged products. Typically, the α-chloro-(or bromo-)lactam† (0.050 mole) is treated with potassium t-butoxide (0.10 mole) in t-butyl alcohol, initially at 50° and then at reflux temperature for 18 hours. The reaction mixture is acidified, the t-butyl alcohol removed by distillation (this procedure hydrolyzes the imino acid ester which is initially formed), and the aqueous residue is extracted with

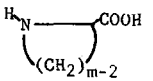
---

*Proline as well as alkyl-substituted prolines have been prepared by treatment of suitable 3-halopiperidin-2-ones with base (4), and pipecolic acid amide by the reaction of 3-chloro-2-oxohexamethylenimine with NH_3 under NH_4Cl catalysis (5). These reactions may possibly represent first examples of the Favorskii rearrangements in the α-halolactam series.

†The α-chloro-(or bromo-)lactams, prepared by halogenation (6) of the lactams to the α,α-dihalo derivatives followed by catalytic hydrogenolysis to the monohalogenated lactams, had satisfactory physical and analytical properties. The lactams themselves were conveniently prepared by the Beckmann rearrangement of the corresponding cycloalkanone oximes.

TABLE I

Cylic α-Imino Acids Homologous to Proline



Compound	m	Name	m.p., °C	Typical Yields %	R_f [a]	Elution Time (min) [b]	Phenylthiohydantoin Derivative m.p., °C
IIId	7	Hexahydroazepine-2-carboxylic Acid	205-208 dec.	43-57	0.28	278	165-166
IIIe	8	Octahydroazocine-2-carboxylic Acid	168-171 dec.	59-67	0.34	333	120-121
IIIf	9	Octahydroazonine-2-carboxylic Acid	156-158 dec.	76-80	0.40	401	152-153
IIIg	10	Decahydroazecine-2-carboxylic Acid	147-148 dec.	22-37	0.48	488	124-126
IIIh	11	Azacycloundecane-2-carboxylic Acid	143-144 dec.	21-34	0.55	666	160-162

[a] Paper chromatography on Whatman No. 1 paper, descending, with water-saturated t-amyl alcohol:2,6-lutidine (1:1) as solvent. Sprayed with a 0.3% solution of ninhydrin in ethanol. Proline and pipecolic acid have R_f 0.13 and 0.17 in this system.

[b] From a 158 cm. column of Spinco 150A ion exchange resin (sulfonated styrene-8% divinylbenzene copolymer) with a pH 4.25 citrate buffer on the Beckman-Spinco automatic amino acid analyzer. When chromatographed simultaneously, proline was eluted in 193 minutes and pipecolic acid in 253 minutes.

methylene chloride to remove non-volatile neutral components. The imino acid is isolated initially as a water-insoluble copper complex, and then liberated by treating a methanol or methanol-chloroform solution of the complex with H_2S (7), or more simply with 8-hydroxyquinoline. The free imino acids are all crystallizable from water-acetone, or methanol-acetone.

That these rearrangement products are cyclic α-imino acids is further adduced by the disappearance of N-H absorptions in their infrared spectra when nitrosated, or upon conversion to their phenylthiohydantoin derivatives (Table I). The spectra of these 1,5-polymethylene-3-phenyl-2-thiohydantoins [ν_{max}^{KBr} 1752-1760 cm^{-1} (amide), 1483-1508 cm^{-1} (thioamide); λ_{max}^{EtOH} 235-237 mμ (log ε 3.86-4.01), 269-271 mμ (log ε 4.00-4.15)] were quite comparable to the spectra of the phenylthiohydantoin derivative of proline [ν_{max}^{KBr} 1762 (C=O), 1505 cm^{-1} (C=S); λ_{max}^{EtOH} 238, 272 mμ (log ε 3.96, 4.14)] and of pipecolic acid [ν_{max}^{KBr} 1750 (C=O), 1510 cm^{-1} (C=S); λ_{max}^{EtOH} 233, 272 mμ (log ε 3.97, 4.14)] which were prepared independently.

2-Hydroxymethylhexamethylenimine (8) when oxidized with acid permanganate gave an imino acid identical to hexahydroazepine-2-carboxylic acid (IIId). Ring homology was indicated by decarboxylation of octahydroazocine-2-carboxylic acid (IIIe) and octahydroazonine-2-carboxylic acid (IIIf) in refluxing cycloheptanone to heptamethylenimine and octamethylenimine, respectively, identified as their phenylthiourea derivatives.

These cyclic α-imino acids were all chromogenic with ninhydrin reagent and migrated on paper in ascending order of R_f values with increasing molecular weights, and were eluted in sequence of increasing molecular weights from a column of cation exchange resin using a pH 4.25 citrate buffer (Table I).

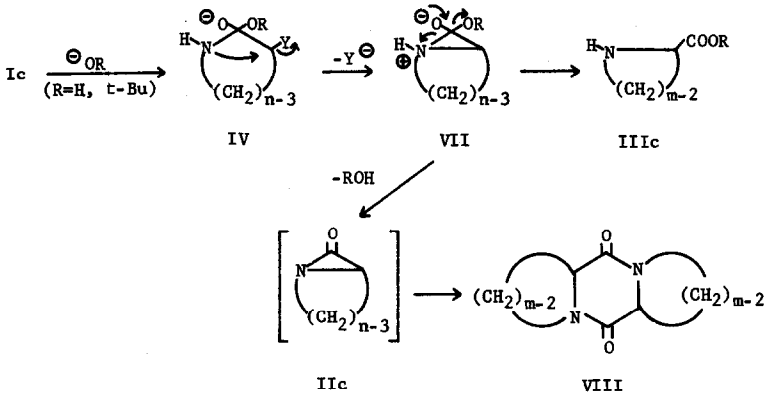
In a few cases, diketopiperazines were isolated as by-products. Thus, treatment of 3-chloro-2-oxoheptamethylenimine (V) with potassium t-butoxide

in tetrahydrofuran gave two isomeric diketopiperazines, $C_{14}H_{22}N_2O_2$, m. pts. 118-119° (19%) and 200-201° (26%), while like treatment of 3-chloro-2-oxoöctamethylenimine (VI) gave two diketopiperazines, $C_{16}H_{24}N_2O_2$, m. pts. 156-158° and 166-168°. These diketopiperazines exhibited amide carbonyl absorptions at approximately 1660 cm^{-1} (KBr) but no N-H absorptions in the infrared, and were hydrolyzable in acid to IIId and IIIe, respectively.

The rearrangement appears not to be initiated by abstraction of the proton on the lactam nitrogen followed by a synchronous 1,3-transannular displacement of the halogen (Loftfield mechanism), since VI did not give rearranged products with NaH, but remained unreacted after 1 hour in refluxing toluene. The isolation of diketopiperazines with NaOH as reagent rules out a semi-benzilic mechanism which cannot account for their formation. A mechanism involving initial hydrolytic cleavage of the lactam ring followed by cyclization of the resulting α-halo-ω-aminoalkanoic acid by intramolecular displacement of halogen by the amino group, while perhaps operating in part in the formation of the 7-membered IIId, is highly improbable in the formation of imino acids of the higher-membered series on the basis of the known difficulty of cyclization of ω-bromoalkylamines to polymethylenimines of medium ring-size (9). This was verified experimentally. Whereas VI gave the 8-membered IIIe in 40% yield with 2.6N NaOH in aqueous dioxan (as well as a diketopiperazine, m.p. 152-154° in 6% yield), the corresponding 2-chloro-8-aminoöctanoic acid (prepared by hydrolysis of the chlorolactam VI in acid) under identical conditions, did not cyclize to IIIe when examined by TLC [95% C_2H_5OH:ØH:H_2O (40:10:10), n-C_4H_7OH:HOAc:H_2O (25:6:25, upper phase) (Cellulose); CH_3OH:H_2O:ØH (35:20:1) (Silica Gel)], although a total of four ninhydrin chromogenic

components were detected.* By contrast, TLC of the reaction mixture from the chlorolactam VI showed only two ninhydrin chromogenic components, one of which proved to be the α-imino acid IIIe.

The following mechanism is tentatively proposed for this rearrangement:



Carbonyl attack by ⊖OR on the α-halolactam Ic followed by a 1,3-transannular displacement of the halogen would give the intermediate VII which may collapse to an α-imino acid (or ester) (IIIc), or eliminate the elements of ROH to give a bicyclic aziridinone IIc, which can further dimerize to the diketopiperazine VIII. All efforts to isolate the aziridinones IIc or identify them in reaction mixtures by infrared analyses under conditions which were successful for the identification of other aziridinones (10) have, however, not yet met with success. Since the stability of aziridinones is largely dependent on the presence of multiple alkyl substituents in positions adjacent to the carbonyl group and the

*However, 2-chloro-7-aminoheptanoic acid on like treatment gave IIId in amounts detectable by TLC. The reaction mixture contained five ninhydrin chromogenic components separable by TLC. These same five products were also detected on treatment of V under identical conditions.

amide nitrogen (10e), the isolation of bicyclic aziridinones may be possible only from suitably substituted α-halolactams.

Acknowledgement

This work was supported in part by USPHS Grant CA 06432.

REFERENCES

1. A. S. Kende, Organic Reactions, Vol. 11, R. Adams et. al, Eds., pp. 261-316. John Wiley and Sons, Inc., New York (1960).
2. A. W. Fort, J. Am. Chem. Soc. 84, 4979 (1962).
3. J. M. Conia and J. Salaun, Tetrahedron Letters 18, 1175 (1963).
4. (a) P. B. Hamilton, J. Biol. Chem. 198, 587 (1952); (b) M. Honjo, J. Pharm. Soc. Japan 78, 888 (1958); (c) T. Takahashi and K. Kariyone, J. Pharm. Soc. Japan 79, 711 (1958).
5. W. C. Francis, J. R. Thornton, J. C. Werner and T. R. Hopkins, J. Am. Chem. Soc. 80, 6238 (1958).
6. R. J. Wineman, E-P. T. Hsu and C. E. Anagnostopoulos, J. Am. Chem. Soc. 80, 6233 (1958).
7. J. P. Greenstein and M. Winitz, Chemistry of the Amino Acids, Vol. 3, p. 2179. John Wiley and Sons, Inc., New York (1961).
8. F. F. Blicke, Chem. Abstr. 50, 5781 (1956).
9. E. L. Eliel, Steric Effects in Organic Chemistry, M. Newman, Ed., pp. 115-116. John Wiley and Sons, Inc., New York (1956).
10. (a) H. E. Baumgarten, R. L. Zey and U. Krolls, J. Am. Chem. Soc. 83, 4469 (1961); (b) H. E. Baumgarten, J. Am. Chem. Soc. 84, 4975 (1962); (c) H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark and R. D. Thompson, J. Am. Chem. Soc. 85, 3303 (1963); (d) J. C. Sheehan and I. Lengyel, J. Am. Chem. Soc. 86, 746 (1964); (e) J. C. Sheehan and I. Lengyel, J. Am. Chem. Soc. 86, 1356 (1964).