The Twelve to Fifteen-membered Ring Homologs of Proline (1)

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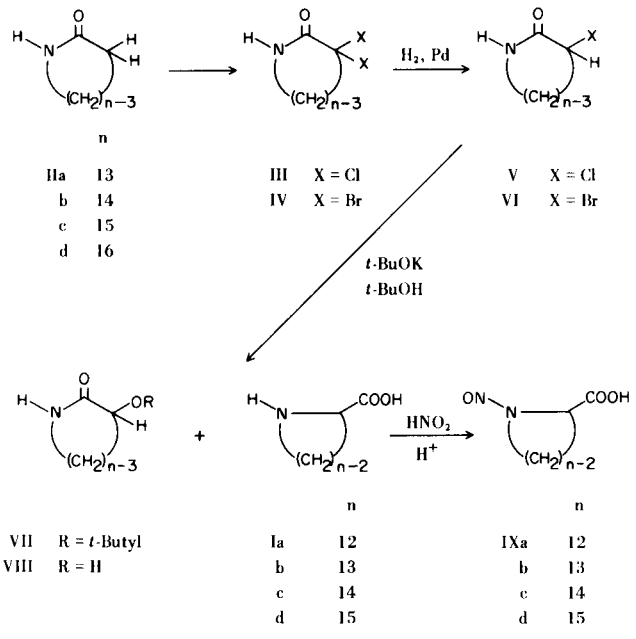
The properties of the homologous series of aliphatic straight-chain α-amino acids from butyrine (C_4) to dodecyline (C_{12}) and including stearine (C_{18}) have been reviewed by Greenstein and Winitz (2). We have previously reported (3) on the synthesis and biological properties of the 7-, 8-, 9-, 10-, and 11-membered medium ring homologs of the naturally occurring cyclic α-imino acid, proline. This work has now been extended to include the imino acids of ring sizes 12 through 15 (Ia-d) in order to ascertain the generality of the Favorskii-like rearrangement utilized for their syntheses. In addition, neutral by-products of these and earlier reactions have been characterized.

As alluded to above, the key reaction leading to these macrocyclic α-imino acids involves the base catalyzed rearrangement (4) of the α-halogenated-ω-aminolactams V (or VI) to I (Scheme 1). The lactams II were all prepared *via* the Beckmann rearrangement (3) of the corresponding alicyclic ketoximes of one lower ring size, except for IIb, which was synthesized from cyclotridecanecarboxylic acid by reaction of the latter with nitrosyl sulfuric acid (5). The lactams II were chlorinated with phosphorous pentachloride in chloroform-toluene (3,6a,b) to give mixtures of the dichlorolactams III and the monochlorolactams V. The dichlorolactams III were isolated by fractional crystallization; the remaining mixture was hydrogenated to reduce the residual III to the monochlorolactams V. The latter are resistant to hydrogenolysis and are readily crystallized from the reduction mixtures. The corresponding dibromo- (IV) and monobromo- (VI) lactams were prepared by bromination of II in chloroform with 2 or 1 moles of bromine with zinc chloride or iodine as catalysts (6b). These halogenated lactams are listed in Table I.

SCHEME I



The rearrangement of the monohalolactams V and VI was effected with potassium *t*-butoxide in *t*-butyl alcohol (3). Whereas the 8- to 10-membered monohalolactams underwent nearly complete rearrangement to ring-contracted products, *viz.*, to α-imino acids and their diketopiperazines (3), rearrangement was no longer complete in this higher membered series and products of nucleophilic displacement, *viz.*, α-*t*-butyloxylactams (VII) and α-hydroxylactams (VIII) were isolated as by-products (Table II). The latter are derived from cleavage of VII during the workup with acid. The well-resolved 1 proton triplet at δ 4.26 (J = 4 Hz) in the nmr spectrum of VIIb verifies the position of the hydroxyl substituent as α. Stuart-Briegleb models of these large ring α-halolactams show that the steric encumbrance at the back side of the carbon atom bearing the halogen substituent is diminished, thereby rendering S_N2 displacements more facile in this series.

The imino acids Ia and Ib were isolated as their insoluble copper complexes and then liberated from the Cu(II) by treatment with 8-hydroxyquinoline. Imino acids Ic and Id did not form copper complexes but were readily isolable due to their insolubility in water at *p*H 7. Although elemental analyses of Ia-d were satisfactory (Table II), they could not be construed as *prima facie* evidence of ring homology, even though their monohalolactam precursors were adequately characterized. However, the mass spectra of Ia-d and their *N*-nitroso deriva-

TABLE I

Halogenated Lactams

Compound Number	Ring Size n	Yield %	Recrystallization Solvent	M.p., °C	Formula	Analyses Calcd. (%) C	H	N	Found (%) C	H	N
IIIa	13	23	Acetone	154-155	$C_{12}H_{21}NOCl_2$	54.14	7.95	5.26	54.38	7.87	5.33
IIIb	14	31	Hexane	136-137	$C_{13}H_{23}NOCl_2$	55.72	8.27	5.00	55.77	8.27	4.87
IIIc	15	16 (a)	Hexane	117-118.5	$C_{14}H_{25}NOCl_2$	57.14	8.56	4.76	57.44	8.57	4.80
IIId	16	13	MeOH	94-96	$C_{15}H_{27}NOCl_2$	58.44	8.83	4.54	58.49	8.71	4.70
IVa	13	78	CH_2Cl_2-hexane	163-163.5	$C_{12}H_{21}NOBr_2$	40.59	5.96	3.94	40.86	5.68	4.11
IVb	14	65	CH_2Cl_2-hexane	144-144.5	$C_{13}H_{23}NOBr_2$	42.30	6.28	3.79	42.59	6.19	4.08
IVc	15	63	CH_2Cl_2-hexane	108-109	$C_{14}H_{25}NOBr_2$	43.88	6.58	3.66	44.16	6.54	3.92
IVd	16	55	CH_2Cl_2-hexane	104-105	$C_{15}H_{27}NOBr_2$	45.36	6.85	3.53	45.06	6.75	3.82
Va	13	33	MeOH	137-138.5	$C_{12}H_{22}NOCl$	62.19	9.57	6.04	62.12	9.44	6.06
Vb	14	78	CH_2Cl_2-Pet ether	127-128	$C_{13}H_{24}NOCl$	63.53	9.84	5.70	63.79	9.68	5.78
Vc	15	68	Hexane	124-126	$C_{14}H_{26}NOCl$	64.72	10.09	5.39	65.02	9.96	5.31
Vd	16	61	MeOH-H_2O	81-83	$C_{15}H_{28}NOCl$	65.79	10.31	5.11	65.74	10.46	5.30
VIa	13	69	CH_2Cl_2-hexane	161-162	$C_{12}H_{22}NOBr$	52.18	8.03	5.07	52.35	7.98	5.04
VIb	14	92	CH_2Cl_2-hexane	154-155	$C_{13}H_{24}NOBr$	53.80	8.33	4.83	54.08	8.23	4.59
VIc	15	82	CH_2Cl_2-hexane	153-153.5	$C_{14}H_{26}NOBr$	55.26	8.61	4.60	55.29	8.77	4.61
VId	16	52	CH_2Cl_2-hexane	130-131	$C_{15}H_{28}NOBr$	56.60	8.87	4.40	56.74	8.96	4.41

(a) Prepared by chlorination of (Vc).

TABLE II

Reaction Products

Compound Number	Ring Size n	Yield %	Recrystallization Solvent	M.p., °C	Formula	Molecular Ion (M^+) (m/e)	Analyses Calcd. (%) C	H	N	Found (%) C	H	N
Ia	12	42	H_2O-Acetone	(a)	$C_{12}H_{23}NO_2$	213	67.57	10.87	6.57	67.86	10.93	6.58
Ib	13	11.5	H_2O-Acetone	(a)	$C_{13}H_{25}NO_2$	227	68.68	11.08	6.16	68.97	11.05	6.34
Ic	14	33	MeOH-H_2O	(a)	$C_{14}H_{27}NO_2$	241	69.67	11.28	5.80	69.71	10.99	5.52
Id	15	16	MeOH-H_2O	(a)	$C_{15}H_{29}NO_2$	255	70.54	11.46	5.48	70.35	11.30	5.79
VII	12 (b)	(c)	Pet ether	96-98	$C_{15}H_{29}NO_2$	255	70.54	11.46	5.48	70.85	11.50	5.56
VIIa	13	6.3	Hexane	94-95	$C_{16}H_{31}NO_2$	269	71.33	11.60	5.20	71.31	11.75	5.31
VIII	11 (b)	11	CH_2Cl_2-Pet ether	124-125.5	$C_{10}H_{19}NO_2$	185	64.83	10.34	7.56	65.11	10.39	7.66
VIII	12 (b)	47	CH_2Cl_2-Pet ether	139-140	$C_{11}H_{21}NO_2$	199	66.29	10.62	7.03	66.11	10.35	6.97
VIIIa	13	19	CH_2Cl_2	136-136.5	$C_{12}H_{23}NO_2$	213	67.57	10.87	6.57	67.56	10.96	6.34
VIIIb	14 (d)	26	CH_2Cl_2-hexane	120-122	$C_{13}H_{25}NO_2$	227	68.68	11.08	6.16	68.69	10.85	5.92
VIIIc	15	18	CH_2Cl_2-hexane	133-134	$C_{14}H_{27}NO_2$	241	69.67	11.28	5.80	69.82	11.55	5.59
VIIId	16	25	CH_2Cl_2-Pet ether	117-118	$C_{15}H_{29}NO_2$	255	70.54	11.46	5.48	70.56	11.41	5.56
IXa	12 (e)	58	CH_2Cl_2-Pet ether	105-106	$C_{12}H_{22}N_2O_3$	242	59.48	9.15	11.56	59.27	9.25	11.25
IXb	13	33	CH_2Cl_2-Pet ether	111-112	$C_{13}H_{24}N_2O_3$	256	60.91	9.44	10.93	61.20	9.45	10.98
IXc	14	63	CH_2Cl_2-Isopentane	117-118	$C_{14}H_{26}N_2O_3$	270	62.19	9.69	10.36	62.48	9.74	10.60
IXd	15	48	CH_2Cl_2-Pet ether	117-119	$C_{15}H_{28}N_2O_3$	284	63.35	9.92	9.85	63.28	10.19	10.05

(a) The imino acid does not melt but slowly decomposes above 180°; (b) These products were isolated but not reported previously (3); (c) No yield is given because the compound was isolated from the combined neutral fractions of 4 separate runs; (d) Nmr (deuteriochloroform): δ 4.26 (t, 1, J = 4 Hz); δ 3.2-3.6 (m, 2); (e) The nitroso imino acids (IX) were prepared by a standard method (10).

tives IXa-d provided persuasive evidence in this regard. Not only did they exhibit readily identifiable molecular ions on electron impact, each of the free α-imino acids Ia-d displayed a prominant M-45 peak (loss of COOH; base peak % Σ_{40} 18-20) analogous to that obtained with proline itself (7). The fragmentation patterns of the *N*-nitroso-α-imino acids were slightly more complex (8), but IXa-d all displayed M-30 peaks due to the loss of NO (9).

EXPERIMENTAL (11)

Azacyclododecane-2-carboxylic Acid (Ia).

3-Bromoazacyclotridecan-2-one (VIa) (27.60 g., 0.100 mole) in 750 ml. of *t*-butyl alcohol was warmed to 52° and potassium *t*-butoxide (16.8 g., 0.15 mole) dissolved in 150 ml. of *t*-butyl alcohol was added. The mixture was heated under reflux for 19 hours, cooled, then acidified with 500 ml. of 1.0 *N* hydrochloric acid. The *t*-butyl alcohol was slowly distilled off (1 hour) and the residue was cooled and extracted with (4 x 125 ml.) of ether. This ether extract was later worked up to yield neutral by-products (*vide infra*).

The aqueous phase was neutralized with sodium carbonate, heated with cupric carbonate (malachite) (11 g., 0.1 mole) for 5 minutes, then cooled and the precipitate collected. The solids were washed with 25 ml. of water and leached with 25 ml. portions of hot methanol-chloroform (1:1) until the extract was no longer colored. The unreacted cupric carbonate which remained was combined with the aqueous filtrate above, and the procedure repeated until no more blue complex was extracted. The combined chloroform-methanol extract was reheated to dissolve the precipitated complex and was filtered hot to remove traces of cupric carbonate. To the filtrate was added 8-hydroxyquiñoline (14.52 g., 0.080 mole) and the mixture was concentrated *in vacuo* to precipitate the copper 8-hydroxyquinolate which was removed by filtration. The filtrate was evaporated to about 100 ml., diluted with 200 ml. water and filtered. The filtrate was extracted with ether and the aqueous phase was decolorized with charcoal and concentrated *in vacuo* nearly to dryness. The viscous residue was diluted with cold acetone to precipitate the product as colorless crystals (Table II).

Azacyclotridecane-2-carboxylic Acid (Ib).

3-Chloroazacyclotetradecan-2-one (Vb) (3.00 g., 0.012 mole) in 40 ml. of *t*-butyl alcohol was heated under reflux with potassium *t*-butoxide (3.0 g., 0.03 mole) in 30 ml. *t*-butyl alcohol for 48 hours and worked up as described for (Ia).

Azacyclotetradecane-2-carboxylic Acid (Ic).

3-Bromoazacyclopentadecan-2-one (VIc) (10.14 g., 0.033 mole) in 100 ml. of *t*-butyl alcohol was heated under reflux with potassium *t*-butoxide (7.0 g., 0.06 mole) in 100 ml. of *t*-butyl alcohol for 18 hours. After acidification with 100 ml. of 1.2 *N* hydrochloric acid, the *t*-butyl alcohol was slowly distilled off (1 hour) and the cooled residue extracted with (4 x 125 ml.) ether. The aqueous phase was concentrated *in vacuo* to *ca.* 100 ml. and neutralized with 6 *N* sodium hydroxide. The voluminous yellow precipitate which formed was collected, washed with 50 ml. of cold water and dissolved in 100 ml. of methanol. The yellow solution was treated with charcoal, filtered, and the filtrate was diluted with 100 ml. of hot water. Enough methanol was added to remove cloudiness. Filtration through a mat of charcoal yielded a colorless filtrate which was concentrated *in vacuo* to give (Ic) in 5 crops which were collected and recrystallized (Table II).

Azacyclopentadecane-2-carboxylic Acid (Id).

3-Chloroazacyclohexadecan-2-one (Vd) (5.48 g., 0.020 mole) in 100 ml. of *t*-butyl alcohol was heated under reflux with potassium *t*-butoxide (5.0 g., 0.045 mole) in 100 ml. of *t*-butyl alcohol for 20 hours. The reaction mixture was worked up as described for Ic.

Neutral By-products (VII) (VIII).

The ether extracts containing acid insoluble by-products from the preparations of I were evaporated to dryness to yield mixtures of α*t*-butyloxylactam (VII) and α-hydroxylactam (VIII). A preliminary separation of VIII was accomplished by fractional crystallization from methylene chloride-hexane. The combined mother liquors containing VII and VIII was charged on a column of alumina (Giulini, Grade II, acid washed) and eluted with methylene chloride [methylene chloride-hexane (1:1) for (VII) (VIIIa)] to give products listed in Table II.

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