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Lactams. II.[1] Synthesis and Acid Hydrolysis of 1-Benzyl-2-piperidone Derivatives Possessing the Carboxyl Function: Equilibrium between 6- and 5-Membered Lactams[2]

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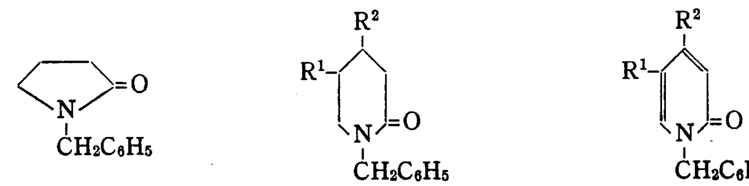
The synthesis and hydrolysis study in boiling 6.04N hydrochloric acid of lactams have been extended to include 1-benzyl-2-pyrrolidinone (I), 1-benzyl-2-oxo-5-piperidineacetic acid (II), 1-benzyl-2-oxo-4-piperidinecarboxylic acid (III), and 1-benzyl-2-oxo-5-piperidinecarboxylic acid (IV). In all cases, the hydrolysis was found to proceed to an equilibrium as shown in Table III. Substituents at the 4- or 5-position of the 2-piperidone ring seemed to favor the lactam form in the lactam–ω-amino acid hydrochloride equilibrium. The lactam form was somewhat more favored in the case of the simple 5-membered lactam (I) than in the case of the simple 6-membered lactam, 1-benzyl-2-piperidone.[1] Such a trend was more evident in the cases of II and III; the 5- and 6-membered lactams were equilibrated in the ratio 4.5:1. It was also observed that III was thermally converted into the 5-membered lactam (XV), whereas II was stable at 180° for 5 hr. Infrared frequency data on several lactams are collected in Table I in order to visualize the lower shift of lactam ν_{CO} exhibited in the solid state by the lactams possessing the carboxyl group else where in the molecule.

Our increasing interest in the recently reported equilibrium[1] between a 6-membered lactam and the correspon ding ω-amino acid hydrochl oride in boiling hydrochlori c acid prompted an investigation with the piperidone derivatives possessing the carboxyl group, which, on acid hydrolysis, would equilibrate with ring-contracted lactam carboxylic acids through ring-opened monoamino dicarboxylic acids. The models selected for synthesis and investigation were 1-benzyl-2-pyrrolidinone (I),[5] 1-benzyl-2-oxo-5-piperidineacetic acid (II), 1-benzyl-2-oxo-4-piperidinecarboxylic acid (III), and 1-benzyl-2-oxo-5-piperidinecarboxylic acid (IV).



I

II: $R^1=CH_2CO_2H$; $R^2=H$
III: $R^1=H$; $R^2=CO_2H$
IV: $R^1=CO_2H$; $R^2=H$

V: $R^1=COCH_3$; $R^2=H$
VI: $R^1=CH_2CSN$(morpholino)O; $R^2=H$
VII: $R^1=CH_2CO_2H$; $R^2=H$
VIII: $R^1=H$; $R^2=CO_2H$
IX: $R^1=CO_2H$; $R^2=H$

Chart 1

1) For article I in this series, see T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970).
2) A section of this work was reported at the 28th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June, 1969.
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5) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

Compound II was synthesized from 1-benzyl-5-acetyl-2(1*H*)-pyridone (V)[1,6] by a reaction sequence patterned after the synthesis of the isomeric 4-piperidineacetic acid derivative.[1,7] Thus, the Willgerodt–Kindler reaction of V using a combination of morpholine, sulfur, and *p*-toluenesulfonic acid as a catalyst[8] produced a crude oil which was presumed to contain 1-benzyl-5-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (VI). The oil was hydrolyzed in boiling aqueous potassium hydroxide to provide 1-benzyl-2-oxo-1,2-dihydro-3-pyridineacetic acid (VII) in an overall yield of 42%. Catalytic hydrogenation of VII leading to II was effected over Raney nickel at 40—45° and atmospheric pressure.

The synthesis of III was accomplished by catalytic hydrogenation of 1-benzyl-2-oxo-1,2-dihydro-4-pyridinecarboxylic acid (VIII)[9] over Raney nickel at atmospheric pressure. Similarly, piperidone IV was prepared from 1-benzyl-2-oxo-1,2-dihydro-5-pyridinecarboxylic acid (IX).[6,10]

Hydrolysis of each of the lactams (I—IV) in boiling 6.04N hydrochloric acid was then studied in the same manner as described previously[1] for 1-benzyl-2-piperidone. Thus, we first followed the progress of the reaction of pyrrolidinone I by measuring the amount of the unchanged lactam. The hydrolysis was found to come to an equilibrium and resulted in about 95% conversion of I into 4-benzylaminobutyric acid hydrochloride (X) in 50 hr, paralleling our experience[1] with 6-membered lactams. The attainment of equilibrium was checked by conducting the reverse experiment with X under the identical reaction condition.

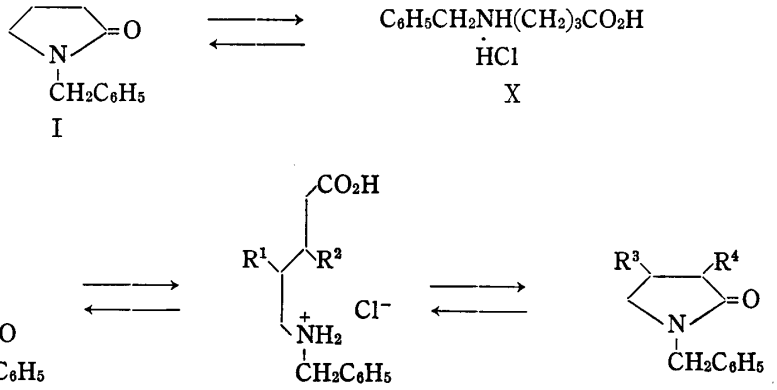

Chart 2

In the hydrolysis of II, it was found that equilibrium among the 6-membered lactam (II) (12%), 3-benzylaminomethyladipic acid hydrochloride (XI) (34%), and the 5-membered lactam, 1-benzyl-2-oxo-4-pyrrolidinepropionic acid (XIV) (54%) was attained in 35 hr. Pyrrolidinone XIV was separated by recrystallization from the lactam fraction containing the unaltered II and the transformed XIV. The infrared (IR) spectrum of XIV in a KBr disk showed strong bands at 1727 (CO_2H) and 1635 cm^{-1} (lactam). Although the frequency of the latter band seemed somewhat low for a simple 5-membered lactam, it was still higher than that of the starting 6-membered lactam (II) by 25 cm^{-1}. In order to fortify such assignment, frequency data on the lactam derivatives obtained in the previous[1] and present studies are collected in Table I. It is of interest that in dilute (0.005M) chloroform solutions all the 6-

6) A. G. Anderson, Jr. and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958).
7) M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **7**, 38 (1959).
8) R. Mayer and J. Wehl, *Angew. Chem.*, **76**, 861 (1964).
9) M. Hasegawa, T. Tatsuno, M. Wataya, and Y. Fujimoto, *Pharm. Bull. Nihon. Univ.* (Tokyo), **3/4**, 41 (1960).
10) S. Sugasawa, S. Akahoshi, S. Toda, and H. Tomisawa, *Yakugaku Zasshi*, **72**, 192 (1952).

membered lactams, regardless of the presence or absence of the carboxyl group, show their ν_{CO} in a region of 1627—1633 cm^{-1}, whereas in the solid state only the piperidones possessing the carboxyl function lower their lactam ν_{CO} by 20—39 cm^{-1}. The analogous relationship is observed also for the 5-membered lactam derivatives; 1674—1683 cm^{-1} in solution and 1635—1649 cm^{-1} in the solid state. Such a lower shift in frequency seems to be caused by intermolecular interaction of the lactam carbonyl group with the carboxyl group as a hydrogen donor, and is reminiscent of the abnormality[11] of carbonyl frequencies found in the secondary and tertiary amides in which carboxyl groups are substituted elsewhere in the molecule.

Table I. Carbonyl Frequencies of Lactams

Compound	Lactam ν_{CO} (cm^{-1})				Carboxyl ν_{CO} (cm^{-1})	
	KBr	Liquid film	$CHCl_3$[a]	$\Delta\nu$[b]	KBr	$CHCl_3$[a]
1-Benzyl-2-piperidone[5]	···	1636	1627	+ 9	···	···
1-Benzyl-4-ethyl-2-piperidone[1]	···	1644	1628	+16	···	···
1-Benzyl-5-ethyl-2-piperidone[1]	···	1643	1630	+13	···	···
1-Benzyl-2-oxo-4-piperidinecarboxylic acid (III)	1595	···	1633	−38	1722	1724
1-Benzyl-2-oxo-5-piperidinecarboxylic acid (IV)	1594	···	1633	−39	1720	1724
1-Benzyl-2-oxo-4-piperidineacetic acid[1]	1598	···	1630	−32	1718	1718
1-Benzyl-6-(3-indolylmethyl)-2-oxo-4-piperidineacetic acid[13h]	1591[13h], 1580[13h]	···	···	···	1695	···
cis-1-Benzyl-6-[(1-methyl-3-iodolyl)-methyl]-2-oxo-4-piperidineacetic acid[13h]	1594[13h]	···	1632[c]	−38	1720[13h]	1715[c]
trans-1-Benzyl-6-[(1-methyl-3-indolyl)-methyl]-2-oxo-4-piperidineacetic acid[13h]	1594[13h], 1584[13h]	···	1631[c]	−37, −47	1719[13h]	1715[c]
1-Benzyl-2-oxo-5-piperidineacetic acid (II)	1610	···	1630	−20	1719	1718
1-Benzyl-2-pyrrolidinone (I)	···	1683	1674	+ 9	···	···
1-Benzyl-2-oxo-4-pyrrolidinepropionic acid (XIV)	1635	···	1683	−48	1727	1718
1-Benzyl-2-oxo-3-pyrrolidineacetic acid (XV)	1649	···	1680, 1632	−31, +17	1716, 1726	1718[d], 1735

a) Measured in ethanol-free $CHCl_3$ at 0.005M concentration.
b) $\Delta\nu=\nu$ (KBr or liquid film) $-\nu$ ($CHCl_3$)
c) Determined in a DMSO solution by Shioiri and Yamada.[13h]
d) shoulder

The 5-membered lactam structure of XIV was also supported by the nuclear magnetic resonance (NMR) spectrum obtained in deuterochloroform. It exhibited a two-proton singlet of the benzylic methylene group at 5.58 τ distinguishable from that of II at 5.44 τ. The difference in the chemical shifts between these two methylene groups paralleled that[12] between the N-methyl groups of the 5- and 6-membered lactams. Table II assembles the chemical shifts and coupling constants of the benzylic methylene protons of the structurally related lactams. Excepting II, every 6-membered lactam having the carboxyl group displays a pair

11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed., Methuen & Co., London, 1958, pp. 211—213.
12) R. M. Moriarty and J. M. Kliegman, *J. Org. Chem.*, **31**, 3007 (1966).

of AB type doublets which reflect magnetic nonequivalence[13] of the methylene protons. It is also interesting to note that the singlet observed in carbon tetrachloride for the benzylic protons of 1-benzyl-4-ethyl-2-piperidone[1] turned AB type pattern in deuterochloroform solution.

Table II. Benzylic Methylene Protons of N-Benzyl-lactams[a]

Compound	Benzylic protons		
	Chemical shift (τ)	Multiplicity[b]	Coupling constant (cps)
1-Benzyl-2-piperidone[5]	5.43	s	...
1-Benzyl-4-ethyl-2-piperidone[1]	5.52 5.36	AB (s)[c]	15 ...
1-Benzyl-5-ethyl-2-piperidone[1]	5.44 (5.54)[c]	s (s)[c]	... ...
1-Benzyl-2-oxo-4-piperidine-carbolxylic acid (III)	5.48 5.32	AB	15
1-Benzyl-2-oxo-5-piperidine-carboxylic acid (IV)	5.57 5.27	AB	15
1-Benzyl-2-oxo-4-piperidineacetic acid[1]	5.47 5.33	AB	15
1-Benzyl-2-oxo-5-piperidineacetic acid (II)	5.44	s	...
1-Benzyl-2-pyrrolidinone (I)	5.57	s	...
1-Benzyl-2-oxo-4-pyrrolidine-propionic acid (XIV)	5.58	s	...
1-Benzyl-2-oxo-3-pyrrolidineacetic acid (XV)	5.58	s	...

a) Unless otherwise stated, the NMR spectra were determined in 8—25% (w/v) $CDCl_3$ solutions.
b) The following abbreviation and convention are used: AB=a pair of AB type doublets, s=singlet.
c) The value and abbreviation in parentheses are those observed in CCl_4 solution.

In following the hydrolysis of II, the amount of each of lactams II and XIV was determined by measuring the area of the corresponding benzylic methylene peaks revealed in the NMR spectrum of the lactam fraction. The progress of the reaction shown in Fig. 1 represents a typical A⇄B⇄C equilibrium.

Similarly, the hydrolysis of compound III proceeded to equilibrium among the 6-membered lactam (III) (4%), 2-(2-benzylaminoethyl)succinic acid hydrochloride (XII) (78%), and the 5-membered lactam, 1-benzyl-2-oxo-3-pyrrolidineacetic acid (XV) (18%) in 30 hr. As given in Tables I and II, butyrolactam XV, which was isolated from the lactam fraction and purified by recrystallization, had the spectral characteristics indicative of the 5-membered structure. In its IR spectrum in a dilute solution, the strong band at 1632 cm^{-1} is still observed besides the unassociated lactam ν_{CO} at 1680 cm^{-1}. The carboxyl ν_{CO} revealed at 1735 cm^{-1} with a shoulder at 1718 cm^{-1} seems slightly higher than that of the other derivatives listed in Table I. The bands at 1632 and 1735 cm^{-1} would be probably due to a molecular species of XV in which intramolecular interaction of the lactam carbonyl group with the proximate carboxyl function[14] is possible. The discrimination in the chemical shifts between the benzylic protons

13) *a*) A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, **1965**, 1241; *b*) P. L. Southwick, J. A. Fitzgerald, and G.E. Milliman, *ibid.*, **1965**, 1247; *c*) K. D. Barrow and T. M. Spotswood, *ibid.*, **1965**, 3325; *d*) J. B. Jones and J. M. Young, *Can. J. Chem.*, **44**, 1059 (1966); *e*) R. W. Horobin, J. McKenna, and J. M. McKenna, *Tetrahedron, Suppl.* **7**, 35 (1966); *f*) R. E. Lyle and J. J. Thomas, *Tetrahedron Letters*, **1969**, 897; *g*) H. Baumann, N. C. Franklin, H. Möhrle, and U. Scheidegger, *Tetrahedron*, **24**, 589 (1968); *h*) T. Shioiri and S. Yamada, *ibid.*, **24**, 4159 (1968); *i*) T. Shioiri, T. Takusagawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 467 (1969).
14) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen & Co., London, 1968, pp. 172—177.

of 5- and 6-membered lactams again made possible the determination of the amount of each of III and XV in the lactam fraction.

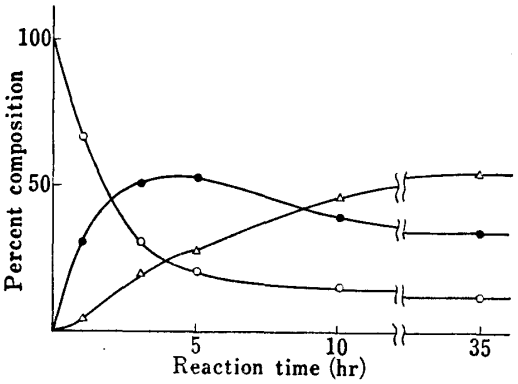

Fig. 1. Composition of Products from Hydrolysis of 0.528M 1-Benzyl-2-oxo-5-piperidineacetic Acid (II) in Boiling 6.04N Hydrochloric Acid

—○—: 1-benzyl-2-oxo-5-piperidineacetic acid (II)
—●—: 3-benzylaminomethyladipic acid hydrochloride (XI)
—△—: 1-benzyl-2-oxo-4-pyrrolidinepropionic acid (XIV)

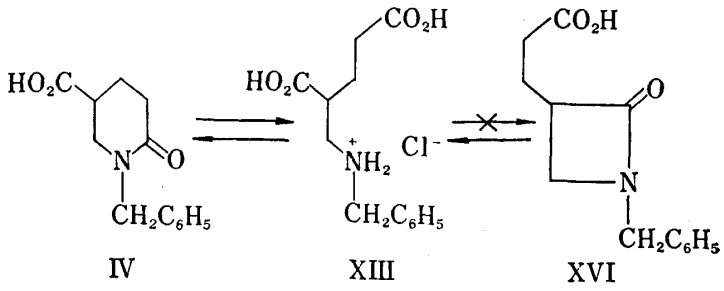

Chart 3

The hydrolysis of piperidone IV was rather rapid and equilibrium between IV (9%) and 2-benzylaminomethylglutaric acid hydrochloride (XIII) (91%) was established in about 5 hr. Since there was no indication that the possible isomeric 4-membered lactam (XVI) was present in the lactam fraction, cyclization of XIII to XVI seemed improbable. Even if it is probable, the equilibrium between XIII and XVI must lie almost completely on the side of XIII.

Compounds X—XIII derived from the hydrolys is of lactams I—IV were characterized as the hydrochloride[15] or N-tosylated ω-amino acids.

It may be seen from Table III that the substituents at the 4- or 5-position of the 2-piperidone ring all produce the shift of equilibrium to the lactam side, being consistent with the previous results.[1] The lactam form seems to be somewhat more favored in the equilibrium between the simple 5-membered lactam (I) and X than in that between 1-benzyl-2-piperidone,[1] the simple 6-membered lactam, and 5-benzylaminovaleric acid hydrochloride. That the 5- and 6-membered lactams were equilibrated in the ratio 4.5:1 in the hydrolysis of II and III would be a reflection of such a tendency.

Table III. Hydrolysis of 0.528M Lactams in Boiling 6.04N Hydrochloric Acid

Lactam	At equilibrium			
	Approx. time (hr)	Component (%)		
		6-Membered lactam	ω-Amino acid hydrochloride	5-Membered lactam
I	50	···	X: 95	I: 5
II	35	II: 12	XI: 34	XIV: 54
III	30	III: 4	XII: 78	XV: 18
IV	5	IV: 9	XIII: 91	···
1-Benzyl-2-piperidone[1]	20	2	98[1]	···

15) It should be noted that 4-benzylaminobutyric acid hydrochloride (X)[19] was so easily esterified that ethanol–ether could not be used for recrystallization.

Further interest in the transformation of a 6-membered lactam into a 5-membered one stems from the thermal conversion of III into XV. When III was heated without solvent in an oil bath kept at 130°, approximately 28% of III was converted into XV in 1 hr; 70%, in 5 hr. However, the reverse experiment with XV under identical reaction condition failed to give any detectable amount of III. These observations remind us of the facile thermal interconversion between the *cis* and *trans* isomers of 2-oxo-5-ethyl-4-piperidineacetic acid.[16] On the other hand, both II and XIV were stable even at 180° for 5 hr.

Experimental[17]

1-Benzyl-2-oxo-1,2-dihydro-5-pyridineacetic Acid (VII)——A mixture of 1.1 g of *p*-toluenesulfonic acid monohydrate and 200 ml of toluene was evaporated to dryness under slightly reduced pressure to obtain the anhydrous acid. To it were added 36.6 g (0.42 mole) of morpholine, 45.5 g (0.2 mole) of ketone V,[1,6] and 6.8 g of sulfur. The mixture was heated at 150—160° (bath temp.) for 3 hr, and then evaporated *in vacuo* to leave a dark oil presumed to contain 1-benzyl-5-morpholinothiocarbonylmethyl-2(1*H*)-pyridone (VI). The oil was heated with a solution of 140 g of KOH in 1 liter of H_2O under reflux for 5 hr. The mixture was treated with charcoal, and filtered in order to remove an insoluble oil. The filtrate was acidified with conc. HCl, and allowed to stand in a refrigerator. The precipitates produced were collected, washed with H_2O, and dried to provide 20.4 g (42%) of the crude VII, mp 142—147°. Recrystallizations from ethanol gave colorless prisms, mp 155—158°. UV λ_{max} mμ (ε): 235 (8150), 301 (4850); λ_{min} 223.5 (6900), 256 (530). IR ν_{max}^{KBr} cm^{-1}: 1725 (CO_2H), 1657 (pyridone). NMR (DMSO-d_6) τ: 6.61 (2H, s, $C\underline{H}_2CO_2H$), 4.92 (2H, s, $NC\underline{H}_2C_6H_5$), 3.59 (1H, d, J=9 cps, $H_{(3)}$), 2.73 (5H, s, C_6H_5), *ca.* 2.66 (d-d partially overlaid with the C_6H_5 signal, $H_{(4)}$), 2.36 (1H, d, J=2 cps, $H_{(6)}$), −2.2 (1H, very b, CO_2H). *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.15; H, 5.61; N, 6.08.

1-Benzyl-2-oxo-5-piperidineacetic Acid (II)——A mixture of a solution of 4.87 g (0.02 mole) of pyridone VII in 16 ml of 10% aq. Na_2CO_3 and 30 ml of H_2O and 2.5 g of Raney Ni W-2 catalyst was hydrogenated at a very slight positive pressure at 40—50°. When the reaction was complete, the catalyst was removed by filtration and the filtrate was acidified with conc. HCl to separate an oil. The oil was extracted with chloroform, washed with H_2O, and dried over anhyd. Na_2SO_4. Removal of the solvent *in vacuo* furnished 4.75 g (96%) of a colorless viscous oil, which solidified when triturated with a small amount of acetone. Recrystallizations from 20% aq. ethanol gave II as colorless prisms, mp 103—105°. UV λ_{max} mμ (ε): 252.5 (157), 258.5 (196), 264.5 (187). IR (Table I). NMR ($CDCl_3$) τ: 5.44 (2H, s, $NC\underline{H}_2C_6H_5$), 2.78 (5H, s, C_6H_5), −1.54 (1H, s, CO_2H). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.98; H, 6.97; N, 5.36.

1-Benzyl-2-oxo-1,2-dihydro-4-pyridinecarboxylic Acid (VIII)——Prepared by the reported method.[9] For purification, the crude pyridone (VIII) was extracted with ethyl acetate by using a Soxhlet extraction apparatus. Evaporation of the solvent and recrystallization of the residue from ethanol provided colorless pillars, mp 224—226° (lit.[9] mp 219—220°). UV λ_{max} mμ (ε): 331 (4200); λ_{min} 273.5 (660). IR ν_{max}^{KBr} cm^{-1}: 3000—2500 (CO_2H), 1702 (CO_2H), 1645 (pyridone). NMR (DMSO) τ: 4.83 (2H, s, $NC\underline{H}_2C_6H_5$), 3.35 (1H, d-d, J=7 and 2 cps, $H_{(5)}$), 3.00 (1H, d, J=2 cps, $H_{(3)}$), 2.68 (5H, s, C_6H_5), 2.11 (1H, d, J=7 cps, $H_{(6)}$), −3.3 (1H, very b, CO_2H). *Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.36; H, 5.04; N, 6.36.

1-Benzyl-2-oxo-4-piperidinecarboxylic Acid (III)——Pyridone VIII was hydrogenated at room temp. in the same way as described above for II, and lactam III obtained in 95% yield was recrystallized from 50% aq. ethanol to give colorless prisms, mp 122—124°. UV λ_{max} mμ (ε): 252.5 (158), 258.5 (194), 264.5 (148). IR (Table I). NMR ($CDCl_3$) τ: 7.91 (2H, m, $H_{(5)}$'s), 7.22 (3H, b, $H_{(3)}$'s and $H_{(4)}$), 6.75 (2H, t, J=6 cps, $H_{(6)}$'s), 5.48 and 5.32 (2H, a pair of AB type d's, J=15 cps, $NC\underline{H}_2C_6H_5$), 2.73 (5H, s, C_6H_5), −0.83 (1H, s, CO_2H). *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.02; H, 6.30; N, 6.10.

1-Benzyl-2-oxo-1,2-dihydro-5-pyridinecarboxylic Acid (IX)——This was prepared by the method of Sugasawa, *et al.*[10] Purification of the resulting crude IX in the same manner as described for VIII produced colorless prisms, mp 205—207° (lit. mp 199—200°,[10] 206—208°,[18] 204—205°[6]). UV λ_{max} mμ (ε): 258 (13600), 306 (4760); λ_{min} 230 (4360), 282 (3300). IR ν_{max}^{KBr} cm^{-1}: 3000—2500 (CO_2H), 1718, 1700 (sh) (CO_2H),

16) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

17) All melting points are corrected. The UV spectra were recorded on a Hitachi EPS-2U spectrophotometer in 95% aq. ethanol. The IR spectra were obtained with a JASCO-DS-301 or -402G spectrophotometer and the NMR spectra were determined with a JEOL-JNM-C-60H spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, DMSO =dimethyl sulfoxide, m=multiplet, q=quartet, s=singlet, sh=shoulder, t=triplet.

1655 (sh), 1640 (pyridone). NMR (DMSO) τ: 4.77 (2H, s, $NCH_2C_6H_5$), 3.52 (1H, d, $J=10$ cps, $H_{(3)}$), 2.67 (5H, s, C_6H_5), 2.15 (1H, d-d, $J=10$ and 3 cps, $H_{(4)}$), 1.40 (1H, d, $J=3$ cps, $H_{(6)}$), −2.48 (1H, very b, CO_2H). *Anal.* Calcd. for $C_{13}H_{11}O_3N$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.09; H, 4.92; N, 6.31.

1-Benzyl-2-oxo-5-pyridinecarboxylic Acid (IV)——Catalytic hydrogenation of pyridone IX was carried out in the same way as described for II, and IV was obtained in 90% yield. For analysis a sample was recrystallized from H_2O to afford colorless needles, mp 157—159°. UV λ_{max} mμ (ε): 252.5 (158), 258.5 (192), 264.5 (148). IR (Table I). NMR ($CDCl_3$) τ: 7.93 (2H, m, b, $H_{(4)}$'s), 7.43 (3H, m, b, $H_{(3)}$'s and $H_{(5)}$), 6.61 (2H, d, $J=7$ cps, $H_{(6)}$s), 5.57 and 5.27 (2H, a pair of AB type d's, $J=15$ cps, $NCH_2C_6H_5$), 2.75 (5H, s, C_6H_5), −2.08 (1H, s, CO_2H). *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.06; H, 6.49; N, 6.19.

1-Benzyl-2-oxo-4-pyrrolidinepropionic Acid (XIV)——A solution of 1.97 g of piperidone II in 15 ml of 20% aq. HCl was refluxed for 35 hr, and then evaporated *in vacuo* to leave an oil. To the oil was added 20 ml of H_2O and the mixture was extracted with chloroform. The chloroform solution was dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to dryness to give 1.28 g of a viscous oil, which was presumed from its IR spectrum [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1716 (CO_2H), 1678 (strong, 5-membered lactam), 1630—1645 (medium, b, 6-membered lactam)] to contain XIV and II. The oil solidified on standing at room temp. for *ca.* 10 days. The solid was recrystallized successively from benzene–hexane (2:1) (twice), 20% aq. methanol (twice), and 20% aq. ethanol (twice) to give colorless pillars, mp 93—96°. UV λ_{max} mμ (ε): 252.5 (148), 258.5 (184), 264.5 (140). IR (Table I). NMR ($CDCl_3$) τ: 5.58 (2H, s, $NCH_2C_6H_5$), 2.80 (5H, s, C_6H_5), −0.85 (1H, s, CO_2H). *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.76; H, 7.03; N, 5.57.

3-(N-Benzyl-*p*-toluenesulfonamidomethyl)adipic Acid——In the procedure described above for XIV, the aq. solution of XI separated from the chloroform layer was stirred with an excess of *p*-toluenesulfonyl chloride under alkaline (NaOH) condition. When the chloride was consumed, the solution was washed with ether, and acidified with 10% aq. HCl. The precipitates were filtered, washed with H_2O, and recrystallized from H_2O to afford colorless needles, mp 141—143°. *Anal.* Calcd. for $C_{21}H_{25}O_6NS$: C, 60.13; H, 6.01; N, 3.34. Found: C, 60.26; H, 5.84; N, 3.46.

1-Benzyl-2-oxo-3-pyrrolidineacetic Acid (XV)——Piperidone III was hydrolyzed with 20% aq. HCl and a mixture of XV and III was isolated in the same way as described for XIV. Successive recrystallizations of the mixture from ethyl acetate, benzene, and 50% aq. ethanol gave III. The mother liquors of these recrystallizations were combined, and evaporated *in vacuo* to dryness. The residue was recrystallized successively from benzene, ethyl acetate–hexane, ethyl acetate, and aq. ethanol to furnish XV as colorless minute dice, mp 92—93°. UV λ_{max} mμ (ε): 252.5 (160), 258.5 (194), 264.5 (148). IR (Table I). NMR ($CDCl_3$) τ: 5.58 (2H, s, $NCH_2C_6H_5$), 2.83 (5H, s, C_6H_5), −1.47 (1H, s, CO_2H). *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.82; H, 6.45; N, 5.77.

2-(2-N-Benzyl-*p*-toluenesulfonamidoethyl)succinic Acid——Prepared from the aq. layer containing XII in the same manner as described above for 3-(N-benzyl-*p*-toluenesulfonamidomethyl)adipic acid. Recrystallizations from 25% aq. acetic acid produced colorless needles, mp 126—127°. *Anal.* Calcd. for $C_{20}H_{23}O_6NS$: C, 59.24; H, 5.72; N, 3.46. Found: C, 59.04; H, 5.73; N, 3.63.

2-(N-Benzyl-*p*-toluenesulfonamidomethyl)glutaric Acid——A mixture of 1.77 g of IV and 15 ml of 20% aq. HCl was refluxed for 10 hr. The solution was evaporated *in vacuo* and 20 ml of H_2O was added to the residue. The mixture was extracted with chloroform in order to remove the unaltered IV and the aq. layer containing XIII was tosylated as described above. The N-tosyl derivative was recrystallized from H_2O to give colorless needles, mp 150—152°. *Anal.* Calcd. for $C_{20}H_{23}O_6NS$: C, 59.24; H, 5.72; N, 3.46. Found: C, 59.06; H, 5.75; N, 3.43.

4-Benzylaminobutyric Acid Hydrochloride (X) and Ethyl 4-Benzylaminobutyrate Hydrochloride——Pyrrolidinone I was hydrolyzed and treated in the same way as above. After removal of the unchanged I, the aq. solution containing X was evaporated *in vacuo*. The residual solid was recrystallized from 98% aq. dioxane to yield colorless scales, mp 172—173° (lit.[19] mp 168—169°). *Anal.* Calcd. for $C_{11}H_{16}O_2NCl$: C, 57.52; H, 7.02; N, 6.09. Found: C, 57.70; H, 7.11; N, 5.84.

When the crude hydrochloride X was recrystallized by dissolving it in a small amount of warm ethanol and adding hot ether to the mixture, the ethyl ester of X was obtained as colorless scales of mp 139—141°. Recrystallizations from dioxane gave an analytical sample, mp 144—145° (lit.[20] mp 156°). IR ν_{max}^{KBr} cm^{-1}: 1720, 1270, 1195 (ester). NMR (DMSO) τ: 8.81 (t, CH_3CH_2), 5.96 (q, OCH_2CH_3), 5.91 (s, $NCH_2C_6H_5$), 2.55 (s, C_6H_5), 0.40 (b, NH_2^+). *Anal.* Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.57; H, 7.82; N, 5.43. Found: C, 60.44; H, 7.93; N, 5.35.

Hydrolysis Study of Lactams I, II, III, and IV——Following the progress of hydrolysis of each of lactams I—IV in boiling 6.04N HCl at 0.528M concentration was carried out in the same manner as described previously.[1] In the cases of II and III, in which the 5- and 6-membered lactams were simultaneously brought

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into the lactam fraction, the amount of each component was estimated by recording the NMR spectrum of the mixture and measuring the area of the benzylic methylene peaks corresponding to the 5- and 6-membered lactams. The results are summarized in Table III and Fig. 1.

Thermal Conversion of III into XV——Without solvent, 120 mg of piperidone III was heated in an oil bath kept at 130° for 1 or 5 hr. There was no change in weight. The composition of the resulting oil was estimated by measuring its NMR spectrum as described above. It was found that approximately 28% of III was converted into XV in 1 hr; 70%, in 5 hr.

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