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Lactams. XX.[1] Decarboxylation of Unsaturated Acids incorporated into Six-Membered Lactam Systems

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The thermal decarboxylation of some unsaturated acids (**1**, **5**, **6**, **8**, and **9**) incorporated into six-membered lactams was examined. Although **8** and **9** did not undergo decarboxylation when heated neat at 175—180°C and 240—245°C, respectively, for 2 h, **1**, **5**, and **6** were decarboxylated in 1,1,2,2-tetrachloroethane at 135°C. The relative ease of the reaction was in the order of $1>6\gg5$. In the case of **1**, the rate-decreasing effects observed on dilution and on the addition of trichloroacetic acid suggest the reaction to be a dimeric intermolecular process.

Keywords——unsaturated lactam acid; pyridonecarboxylic acid; cyclic dimer; thermal decarboxylation; hydrogen bond; protonation; dimeric transition state; IR

During the course of our studies[2,3] on the structure of 1-benzyl-5-ethyl-1,2,5,6-tetrahydro-2-oxo-4-pyridineacetic acid (**1**), an intermediate in earlier steps[4] of our recent racemic syntheses of the Ipecac and *Alangium* alkaloids[5] and structurally parallel indoloquinolizidine alkaloids,[6] we found[2] that on heating at 130—140°C for 40 min this unsaturated acid readily underwent decarboxylation to give a 52:48 mixture of the isomeric unsaturated lactams **3** and **4** in 96% yield. This decarboxylation seemed unusually easy by comparison with that reported[7] for simple β,γ-unsaturated acids, but it was assumed[2] to proceed through a six-membered transition state (**2**) by analogy with the usual cyclic intramolecular process.[7] However, the structure of **1** is unique in that the β,γ double bond and the lactam carbonyl group are conjugated, and participation of the transition state **2** in such a facile decarboxylation would be insignificant since the lowered electron density at the β,γ double bond should retard the abstraction of the hydrogen atom from the carboxyl group. In the hope of learning more about the effect of the lactam carbonyl group and of identifying the actual mechanism for the decarboxylation of **1**, we investigated the thermal decarboxylation of some structurally related lactam acids.

The substrates covered by initial studies were **5**,[2] **6**,[8] **8**,[9] and **9**,[9] and they were separately heated neat under an atmosphere of nitrogen at temperatures higher than their melting points by *ca.* 20°C. The pyridone-4-acetic acid **6** underwent decarboxylation very easily at 170—175°C in 1 h, giving the 4-methylpyridone **7** in 97% yield. In the reaction of **5** at 180°C for 4 h, **4** was obtained in 21% yield with 61% recovery of **5**. The formation of **4** can be interpreted in terms of the known isomerization[2] of the normally decarboxylated product **3**. However, the possibility of slow isomerization of **5** to **1** followed by rapid decarboxylation of the latter to **3** and hence to **4** cannot be ruled out. When the above decarboxylation was effected with easy access of air, a small amount of an oily dehydrogenated product presumed to be **20** was obtained as well as a little **4**. On the other hand, the substrates **8** and **9** completely failed to decarboxylate when heated for 2 h at 175—180°C and 240—245°C, respectively. In order to compare the decarboxylation rates roughly, compounds **1**, **5**, and **6** were separately heated in $Cl_2CHCHCl_2$ under identical conditions (135°C, 20 min), and the extent of decarboxylation was estimated by product analysis. Table I summarizes these and the above results. It may be seen that among the five substrates only three, namely, **1**, **6**, and **5**,

are susceptible to thermal decarboxylation. The ease with which decarboxylation occurs decreases in the order of **1**>**6**≫**5**. The presence of the lactam carbonyl group conjugated with the β,γ double bond in the first two of the series suggests that the lactam C=O plays an important role in the reaction.

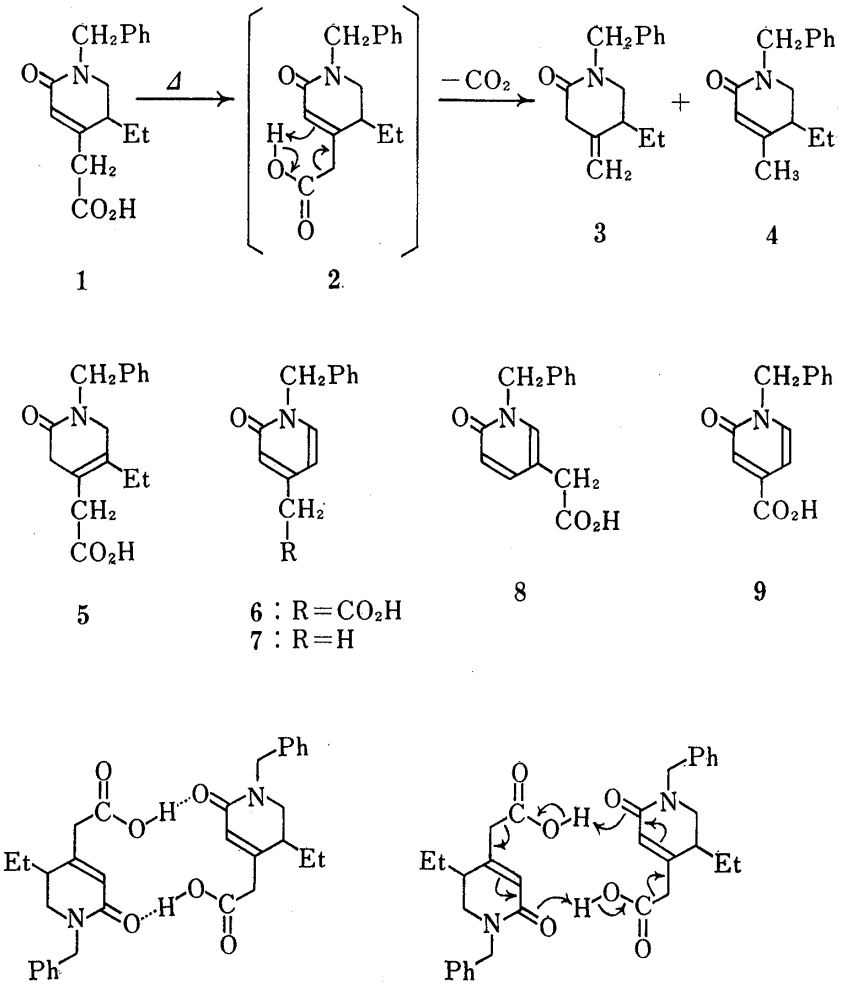


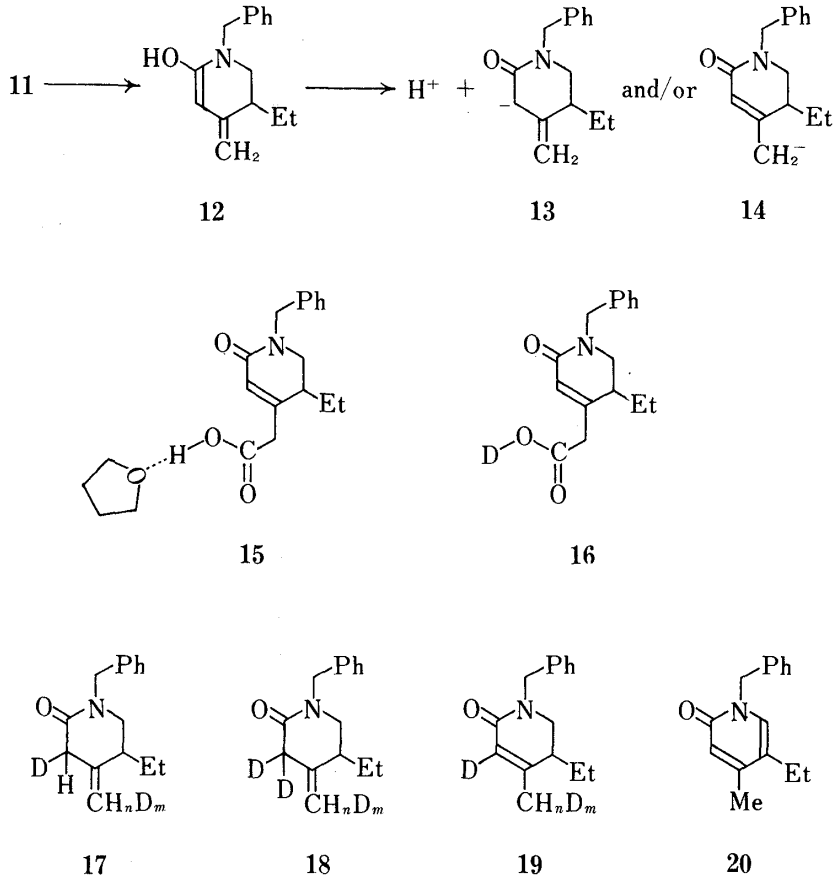
Chart 1

TABLE I. Decarboxylation of Unsaturated Lactam Acids

Lactam acid		Reaction conditions			Product		Recovery of lactam acid (%)
No.	mp (°C)	Solvent	Temp. (°C)	Time (min)	No.	Yield (%)	
1	126—127[a]	nil	130—140	40	**3**+**4**	96[b]	—
1		$Cl_2CHCHCl_2$[c]	135	20	**3**+**4**	44	55
5	153—154	nil	180	240	**4**	21	61
5		$Cl_2CHCHCl_2$[c]	135	20	**3**+**4**[d]	—	91
6	160—161[e]	nil	170—175	60	**7**	97	—
6		$Cl_2CHCHCl_2$[c]	135	20	**7**	25	74
8	155—158	nil	175—180	120	—	—	100
9	224—226	nil	240—245	120	—	—	83

a) With slight effervescence.
b) From ref. 2.
c) Five ml of the solvent was used for 0.5 mmol of the lactam acid.
d) In addition, the presence of unidentified neutral substances was indicated on TLC analysis.
e) With decomposition. The melting point is variable depending on the rate of raising the temperature.[8]

At this point in the present work, the results of X-ray analysis of a single crystal of **1** became available. As reported previously,[3] the analysis disclosed that the carboxylic hydroxyl and the lactam carbonyl group in the molecule **1** form hydrogen bonds with the lactam carbonyl and the carboxyl group, respectively, of another molecule, producing a cyclic dimer (**10**). Such an intermolecular interaction of the lactam C=O with COOH as a hydrogen donor had also been suggested[2,9] on the basis of our infrared (IR) spectroscopic study of six- and five-membered lactams carrying a carboxyl function. In view of these results and the extended conjugation system in **1**, we now consider that the decarboxylation of **1** probably involves the dimeric transition state **11**, from which the formation of **3** and **4** is possible through **12** and **13** and/or **14** (Chart 2).



12 **13** **14**

15 **16**

17 **18** **19** **20**

Chart 2

If the above dimeric transition state mechanism is operative, the rate of the decarboxylation of **1** in solution should be dependent on the concentration of **1** and on the concentration of an extra acid when it is added. To check this, solutions of **1** in $Cl_2CHCHCl_2$ at various concentrations were separately heated at 135°C with or without CCl_3CO_2H, a strong acid soluble in the solvent used. The progress of the decarboxylation was followed by measuring the amount of the unchanged lactam acid **1**. It may be seen from Table II that in the absence of CCl_3CO_2H the rate of decarboxylation decreased as the concentration of **1** was lowered. Clearly, the addition of CCl_3CO_2H caused a retardation of the decarboxylation. This must be due to protonation of **1** at the lactam C=O group[10] with a proton dissociated from CCl_3CO_2H, which overcomes the cyclic hydrogen bonding in **10**, an immediate precursor for the dimeric transition state **11**. The substrate **1** has been prepared from an isomeric mixture of ethyl (1-benzyl-2-oxo-5-ethyl-4-piperidylidene)cyanoacetate by acid hydrolysis (boiling

TABLE II. Decarboxylation of **1** in $Cl_2CHCHCl_2$ at 135°C

Concentration		Reaction time (min)	Decarboxylation (%)
Substrate (**1**) (M)	CCl_3CO_2H (M)		
0.2	nil	17	50
0.2	0.2	35	50
0.2	2	300	14
0.05	nil	25	50
0.005	nil	79	50
0.005	0.005	87	50

TABLE III. Infrared Group Frequencies of **1**

Solvent	Concentration (M)	ν_{max} (cm^{-1})		
		Lactam C=O[a]	C=O[a]	Carboxyl C=O
Nujol[b]	mull	1576	1658	1710
Tetrahydrofuran	0.4	1597, 1628	1672	1732
	0.2	1598, 1628	1671	1732
	0.1	1600, 1628	1672	1732
	0.05	1626	1670	1732
	0.01	1626	1670	1732
$Cl_2CHCHCl_2$	0.2	1590	1660	1715
	0.005	1590[c]	1658	1715, 1745[d]
	0.002	1581, 1611[d]	1660	1720, 1743[d]
	0.001	1592, 1612	1663	1723, 1745

a) See the text and ref. 2 for the assignment of this band.
b) Data taken from ref. 3.
c) Broad.
d) Shoulder.

AcOH–aq. HCl, 15 h).[4a,d] It is now clear why it survives such a vigorous treatment without any significant decarboxylation.

Table III assembles the IR frequencies of the lactam and the carboxyl C=O and the C=C group of **1**. The appearance of strong bands at 1576 cm^{-1} (lactam $\nu_{C=O}$) and 1710 cm^{-1} (carboxyl $\nu_{C=O}$) in the solid state is regarded as a reflection of intermolecular hydrogen bonding of the cyclic dimer **10**. On the other hand, the two lactam $\nu_{C=O}$ bands observed in tetrahydrofuran solutions at 0.1—0.4 M concentration suggest the coexistence of the cyclic dimer **10** and/or hydrogen-bonded linear polymers and the solvated monomer **15** in which the lactam carbonyl is free. On dilution to 0.01—0.05 M, the population of the first and/or the middle species seems to be superseded in importance by that of **15**. The absence of change in the carboxyl $\nu_{C=O}$ and in the $\nu_{C=C}$ on dilution supports not only the presence of the species **15** but also the correctness of the assignment of lactam $\nu_{C=O}$ and $\nu_{C=C}$, which is opposite to what has been suggested[11] for six-membered α,β-unsaturated lactams. The lactam $\nu_{C=O}$ frequency observed in $Cl_2CHCHCl_2$ solution indicates that a fairly large population of hydrogen-bonded species such as **10** still exists even at 0.005 M concentration. This may explain why decarboxylation of **1** occurred rather quickly even in 0.005 M solution in $Cl_2CHCHCl_2$ (Table II).

Finally, deuterium labeling was used to examine the fate of the carboxyl hydrogen atom of **1**. When the labeled acid **16**, generated *in situ* from **1** and D_2O, was heated in $Cl_2CHCHCl_2$ or dimethyl sulfoxide at 135°C or 145°C or under reflux for 15 min–8 h, mixtures consisting of **17**, **18**, and **19** in various ratios were obtained. Since the distribution of deuterium seemed to be complicated by possible scrambling[7] of the label from the carboxyl group prior to decar-

boxylation, this approach was of no further help in the study of the decarboxylation mechanism of **1**.

In conclusion, the present results suggest that the thermal decarboxylation of **1** is a cyclic intermolecular process involving a dimeric transition state (**11**). Hydrogen bonding between the carboxyl and the α,β-unsaturated lactam carbonyl group probably allows the molecule **1** to pass to the transition state **11** much more easily than to the monomeric transition state **2**, and this explains the unusually easy decarboxylation of **1**. A similar mechanism may be operative in the thermal decarboxylation of **6**.

Experimental

General Notes——All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. The solvent $Cl_2CHCHCl_2$ used in this study was purified by distillation using a Perkin-Elmer 251 auto annular still, and its purity was checked by gas–liquid chromatography. Unless otherwise stated, IR spectra were recorded on a JASCO IRA-2 spectrophotometer in $CHCl_3$ solution at 0.2 M concentration. Mass spectra were measured with a JEOL JMS-01SG mass spectrometer. NMR spectra were obtained with a JEOL JNM-FX-100 spectrometer at 24°C with Me_4Si as an internal standard ($\delta=0$ ppm). The following abbreviations are used: d=doublet, d-d=doublet-of-doublets, m=multiplet, q=quartet, s=singlet, t=triplet. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University.

Decarboxylation of 5 to 3 and/or 4——i) Compound **5**[2] (100 mg, 0.366 mmol) was heated neat under an atmosphere of N_2 at 180°C for 4 h. After cooling, the reaction mixture was dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ solution was washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhyd. Na_2SO_4, and concentrated *in vacuo* to leave **4** (18 mg, 21%) as a brownish oil. This sample was identical [by comparison of IR spectrum and thin-layer chromatographic (TLC) behavior] with authentic **4**.[2] The aq. $NaHCO_3$ washings described above were made acidic (pH 1) with 10% aq. HCl. The crystals that resulted were filtered off, washed with a little H_2O, and dried to recover the starting material **5** (61 mg, 61%). When the above decarboxylation was effected with easy access of air, a small amount of an oily dehydrogenated product [MS *m/e*: 227 (M^+); IR $\nu_{max}^{CHCl_3}$ 1666 cm^{-1} (pyridone); NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7.4 Hz, $CH_2\underline{Me}$), 2.15 (3H, d, J=1.0 Hz, 4-Me), 2.35 (2H, q, J=7.4 Hz, $C\underline{H}_2Me$), 5.11 (2H, s, $C\underline{H}_2Ph$), 6.44 (1H, dull s, $H_{(3)}$), 6.93 (1H, s, $H_{(6)}$), 7.29 (5H, s, Ph)] presumed to be 1-benzyl-5-ethyl-4-methyl-2(1*H*)-pyridone (**20**) was obtained as well as a little **4**.

ii) A stirred suspension of **5**[2] (137 mg, 0.5 mmol) in $Cl_2CHCHCl_2$ (5 ml) was heated at 135°C (inner temp.) for 20 min. It became a clear solution in the first 2 min. The reaction mixture was cooled rapidly and concentrated *in vacuo*. The residue was partitioned between $CHCl_3$ (10 ml) and sat. aq. $NaHCO_3$ (6 ml). The $CHCl_3$ extracts were dried and concentrated *in vacuo* to leave an orange oil (8 mg). TLC analysis of the oil indicated that it was a mixture of **3**, **4**, and unidentified substances. On the other hand, the aq. $NaHCO_3$ extracts described above were brought to pH 1 by addition of 10% aq. HCl. The crystals that resulted were filtered off, washed with a little H_2O, and dried to recover **5** (125 mg, 91%), which was identified by comparison with an authentic sample.[2]

Decarboxylation of 6 to 1-Benzyl-4-methyl-2(1*H*)-pyridone (7)——i) Compound **6**[8] (500 mg, 2.06 mmol) was heated neat for 1 h under an atmosphere of N_2 in an oil bath kept at 170—175°C, leaving **7** (398 mg, 97%) as a solid, which was shown to be homogeneous on TLC analysis. Recrystallization of the solid from hexane yielded an analytical sample as colorless needles, mp 64—66°C; MS *m/e*: 199 (M^+); IR $\nu_{max}^{CHCl_3}$ 1664 cm^{-1} (pyridone); NMR ($CDCl_3$) δ: 2.16 (3H, d, J=1.0 Hz, Me), 5.11 (2H, s, $C\underline{H}_2Ph$), 5.98 (1H, d-d, J=7.0 and 2.0 Hz, $H_{(5)}$), 6.41 (1H, m, $H_{(3)}$), 7.13 (1H, d, J=7.0 Hz, $H_{(6)}$), 7.30 (5H, s, Ph). *Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.28; H, 6.62; N, 7.00.

ii) A stirred suspension of **6**[8] (122 mg, 0.5 mmol) in $Cl_2CHCHCl_2$ (5 ml) was heated at 135°C (inner temp.) for 20 min. It became a clear solution within the first 2 min. The reaction mixture was worked up in a manner similar to that described above for **5** under item (ii), affording **7** (25 mg, 25%) as a pale yellowish oil and **6** (90 mg, 74%) as a colorless solid, mp 159.5—160.5°C (dec.). The two substances were identified by comparison of their IR spectra and TLC behavior with those of corresponding authentic samples.

Thermal Treatment of 8——Compound **8**[9] (50 mg) was heated neat for 2 h under an atmosphere of N_2 in an oil bath kept at 175—180°C, leaving a solid without any loss in weight. The IR spectrum of the solid was identical with that of authentic **8**.[9]

Thermal Treatment of 9——Compound **9**[9] (100 mg) was heated at 240—245°C for 2 h as described above for **8**, and a brown solid was obtained without any loss in weight. The solid was partitioned between benzene and 10% aq. NaOH. The aq. NaOH extracts were made acidic (pH 1) with 10% aq. HCl. The pale yellowish precipitate that resulted was collected by filtration, washed with a little H_2O, and dried to recover **9** (83 mg, 83%), mp 220—225°C, which was identical (by comparison of IR spectrum) with an authentic sample. No material was obtained from the benzene extracts described above.

Decarboxylation of 1 in $Cl_2CHCHCl_2$——i) A stirred solution of **1**[2] (137 mg, 0.5 mmol) in $Cl_2CHCHCl_2$ (5 ml) was heated at 135°C (inner temp.) for 20 min. The reaction mixture was worked up as described above for **5** under item (ii), yielding a pale orange, oily mixture (50 mg, 44%) of **3** and **4** with some recovery of **1** (76 mg, 55%), mp 124—125°C (slight effervescence). These materials were identified by comparison of their TLC mobilities and/or IR spectra with those of authentic samples.[2]

ii) Solutions of **1** in $Cl_2CHCHCl_2$ at 0.2, 0.05, and 0.005 M concentrations were separately heated at 135°C (inner temp.) with or without an appropriate amount of CCl_3CO_2H. At intervals, small aliquots of the reaction solutions were taken out, cooled rapidly, and the amount of unchanged **1** was determined by means of high-performance liquid chromatography (HPLC). The HPLC analyses were carried out on a Waters ALC/GPC 204 liquid chromatograph [Porasil A or B, or Bondapak C_{18}, CH_2Cl_2–MeOH (4: 1, v/v) or MeCN–H_2O (1: 1, v/v), 150—1000 p.s.i.], and the peak height of **1** was measured. The amount of **1** was then estimated from calibration curves which had been constructed by the use of an analytical sample. In the case of the reaction solution containing a large amount of CCl_3CO_2H, it was concentrated *in vacuo* and the residue was dissolved in benzene. The benzene solution was washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhyd. Na_2SO_4, and concentrated *in vacuo*, and the residual decarboxylated product was weighed. The results are summarized in Table II.

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