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Lactams. XXIV.[1] Alkaline Hydrolysis of 1-Benzyl-2-piperidone Derivatives: Application to *cis–trans* Isomerization of the 5-Ethyl-2-oxo-4-piperidineacetic Acid System[2]

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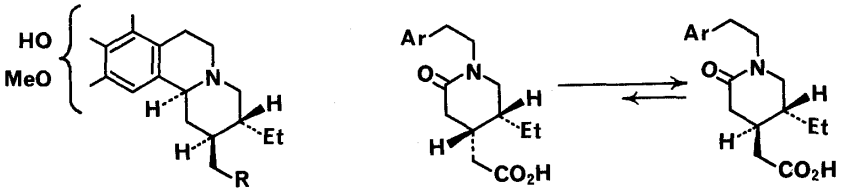
In boiling 2.5 N solution of KOH in 40% (w/w) aqueous EtOH, the lactams (±)-**5a**, **b**, **d** were hydrolyzed to an extent of 75—98% within 8—20 h, attaining equilibrium with the corresponding ω-amino acid derivatives (±)-**6a**, **b**, **d**. The potassium salt (±)-**8**, generated *in situ* from the *trans*-lactam acid (±)-**7**, was equilibrated with the ring-opened product (±)-**6f** and the recyclized *cis* isomer (±)-**5f** in a ratio of 57 : 15 : 28 within *ca.* 45 h under similar reaction conditions. The *cis*-*N*-(2-arylethyl) analog (−)-**9** was converted into the *trans*-lactam acid (+)-**13**, a key synthetic precursor for the 8-hydroxy-9,10-dimethoxybenzo[*a*]quinolizidine-type *Alangium* alkaloids, through application of such alkaline hydrolytic *cis–trans* equilibration followed by debenzylation.

Keywords——lactam alkaline hydrolysis; lactam–ω-amino acid equilibrium; equilibrium substituent effect; lactam acid *cis–trans* equilibration; benzyl ether debenzylation; ^{13}C-NMR stereoisomer determination

The cincholoipon-incorporating strategy employed in our chiral syntheses of the benzo[*a*]quinolizidine-type *Alangium* alkaloids (type **1**)[3] has featured the utilization of the latent molecular symmetry present in the 5-ethyl-2-oxo-4-piperidineacetic acid system (type **2**), derived from the *Cinchona* alkaloid cinchonine *via* cincholoipon ethyl ester, for *cis* → *trans* isomerization (**2**→**3**).[4] We found that such isomerization was feasible through the *cis–trans* equilibration (*e.g.*, **2**⇄**3**) under acid hydrolytic conditions,[4a,5] or less efficiently



1 : R=CH_2OH or a heterocyclic moiety — 2 — 3

Chart 1

under Fischer–Speier esterification conditions at a high temperature (in the case of the *N*-unsubstituted analog),[6] or most efficiently under thermal conditions (*e.g.*, heating at 180 °C without solvent).[1,4,5] The thermal *cis* → *trans* isomerization was assumed to proceed by intramolecular acidolysis of the lactam bond with the exocyclic carboxyl group,[1,5] whereas that under acid hydrolytic or esterification conditions was considered to occur by ring opening through hydrolysis or alcoholysis followed by rotation and recyclization with another carboxyl or alkoxycarbonyl group.[5,6] Since a lactam bond should also be cleavable under basic conditions, alkaline hydrolytic *cis* → *trans* isomerization of the same ring system

should be possible through a similar ring-opened intermediate. In the present work, we thus investigated the alkaline hydrolysis of some model compounds (type **5**) as well as that of the *N*-(2-arylethyl) analog (−)-**9**, a key intermediate[4b-d] for the syntheses of the *Alangium* alkaloids ankorine, alangicine, and alangimarckine.

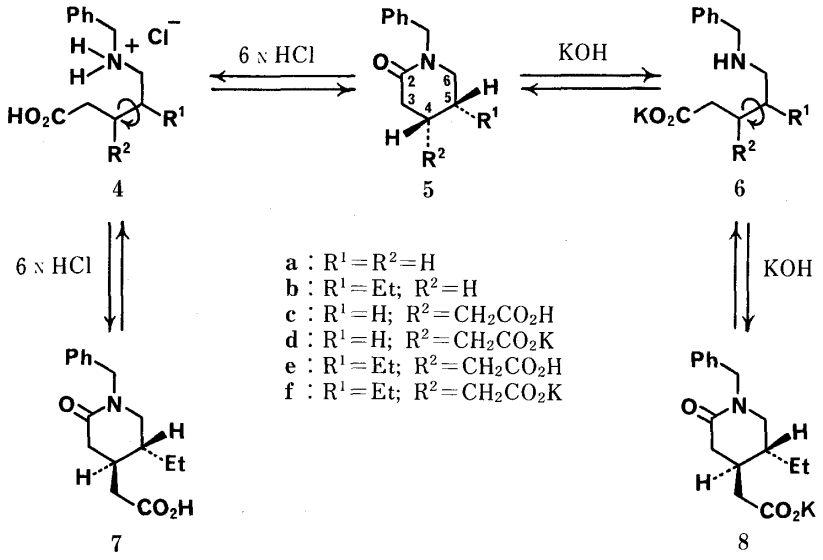


Chart 2

The models selected for the hydrolysis study were 1-benzyl-2-piperidone (**5a**),[7] (±)-1-benzyl-5-ethyl-2-piperidone (**5b**),[8] (±)-1-benzyl-2-oxo-4-piperidineacetic acid (**5c**),[8] and (±)-*trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid (**7**),[5,9] in which the essential partial structures of **2** and **3** are obvious, and they were prepared according to the previously reported procedures.[5,7-9] We first followed the progress of the hydrolysis of **5a** in boiling 2.5 N solution of KOH in 40% (w/w) aqueous EtOH by measuring the amount of the unaltered lactam. The reaction was found to attain equilibrium within *ca.* 18 h and resulted in 98% conversion of **5a** into potassium 5-benzylaminovalerate (**6a**), which was characterized as 5-(*N*-benzylbenzamido)valeric acid. The attainment of equilibrium was also checked by conducting the reverse experiment with **6a**. The alkaline hydrolyses of the other models, **5b** and the potassium salt **5d** generated *in situ* from **5c**, were also studied under similar reaction conditions and found to come to equilibria with the ring-opened derivatives **6b** and **6d**, which were characterized as the *N*-tosyl derivative and the hydrochloride of the corresponding ω-amino acid, respectively. Table I summarizes these results and those obtained previously with the same models under acid hydrolytic conditions. It may be seen that under alkaline conditions all lactams are hydrolyzed to an extent of 75—98% within 8—20 h, attaining equilibria with the corresponding ring-opened derivatives. A substituent at either the 4- or 5-position tends to cause the lactam–ω-amino acid equilibrium (**5**⇄**6**) to shift to the left. This substituent effect is similar to that observed for the same substrates under acidic conditions.[8] In the case of **5c**, however, alkaline hydrolysis is faster than acid hydrolysis. The observation of retention or formation of the lactam bond under alkaline hydrolytic conditions is understandable in the light of the previous study of the glutamic acid–pyroglutamic acid equilibrium.[10]

Next our attention was focused on the problem of hydrolysis of **7**. Thus, the potassium salt **8** generated *in situ* from **7** was treated with KOH in aqueous EtOH under conditions similar to those employed for the other models (**5a,b,d**), and the progress of hydrolysis was followed by measuring the amount of the recovered lactam. In addition, the quantitative

TABLE I. Hydrolysis of Lactams (**5a**—**c**)

Lactam	Alkaline hydrolysis[a]		Acid hydrolysis[b]	
	At equilibrium		At equilibrium[c]	
	Time (h)	% hydrolysis	Time (h)	% hydrolysis
5a	*ca.* 18	98	*ca.* 20	98
5b	*ca.* 20	75	*ca.* 20	74
5c	*ca.* 8	86	*ca.* 15	81

a) Starting with 0.2 M concentration of a lactam in boiling 2.5 N solution of KOH in 40% (w/w) aqueous EtOH. *b*) Starting with 0.528 M concentration of a lactam in boiling 6.04 N aqueous HCl. *c*) Taken from ref. 8.

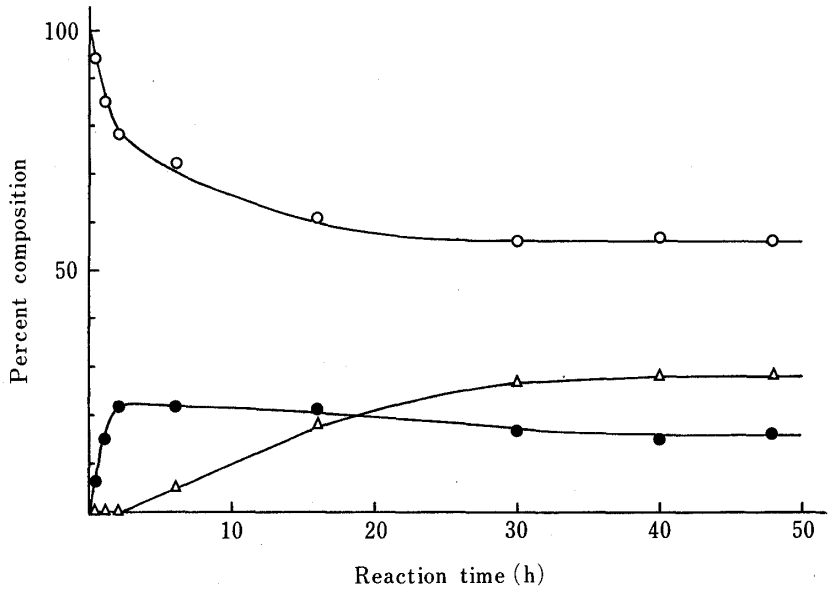


Fig. 1. Variation of the Product Composition with Time in the Hydrolysis of (±)-**7** (**8**) in Boiling 2.5 N Solution of KOH in 40% (w/w) Aqueous EtOH

—○—, the *trans* isomer (±)-**7** (**8**) (initial concentration: 0.2 M); —●—, the ring-opened product (±)-**6f**; —△—, the *cis* isomer (±)-**5e** (**5f**).

analysis of the *cis* and *trans* isomers in the lactam fractions was carried out according to the previously reported carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopic method,[1,4a,b,5,6] which proved most satisfactory (accurate to ±1%) and convenient among those tested. As shown in Fig. 1, a rapid decrease of the amount of the *trans* isomer **7** (**8**) and the appearance and rapid increase of the ring-opened derivative **6f** were observed at earlier stages of the reaction along with the formation of the *cis* isomer **5e** (**5f**) after an induction period, and equilibrium (**8**:**6f**:**5f**=57:15:28) was eventually attained in *ca.* 45 h. This indicates that the *cis–trans* equilibration of the system proceeds through the ring-opened intermediate **6f**, as anticipated. Interestingly, the ratio of the amounts of the three components at equilibrium is the same as that observed previously[5] for the acid hydrolysis (in boiling 6 N aqueous HCl), which comes to equilibrium somewhat faster (within *ca.* 28 h), however. The observed 1:2 ratio of the *cis* to the *trans* isomer in the equilibrated lactam mixture is also the same as that reported[1,5] for the thermal equilibration.

Finally, such alkaline hydrolysis was applied to *cis* → *trans* isomerization of the *N*-(2-arylethyl) analog (−)-**9**. Treatment of (−)-**9** with boiling 2.5 N solution of KOH in 40% (w/w)

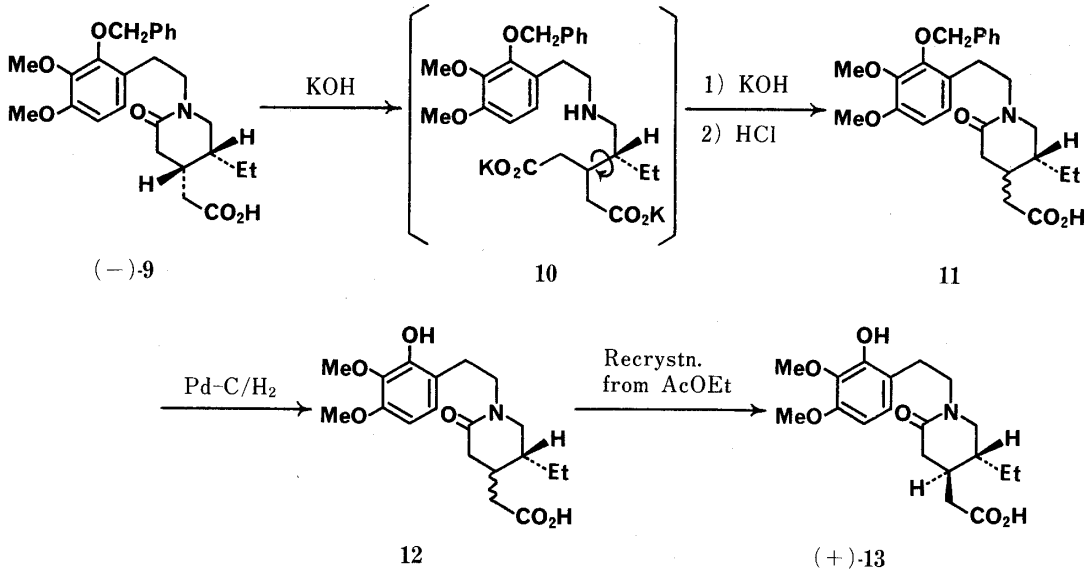


Chart 3

aqueous EtOH for 96 h gave a 49 : 51 mixture[11] of the *cis*- and the *trans*-lactam acids **11** in 95% yield. Although we failed to isolate the ring-opened intermediate **10** in any form, its formation was estimated to be *ca.* 5% on the basis of the amount of the recovered lactam **11**. Since the separation of the stereoisomeric mixture **11** into the two isomers by crystallization or chromatography was difficult, **11** was debenzylated by catalytic hydrogenolysis to afford the phenolic lactam acid **12** (98% yield), from which the desired *trans* isomer (+)-**13** was isolated in 38% yield by recrystallization.

In conclusion, it should be emphasized that the present alkaline hydrolysis represents an alternative method when *cis* → *trans* isomerization of the 5-ethyl-2-oxo-4-piperidineacetic acid system carrying an acid-labile or thermolabile *N*-substituent is required.

Experimental

General Comments——All melting points are corrected. See ref. 1 for details of instrumentation and measurements.

Materials——The substrates used in the alkaline hydrolysis study were prepared according to the reported procedures: 5-benzylaminovaleric acid hydrochloride (**4a**);[7,8] 1-benzyl-2-piperidone (**5a**);[7] (±)-1-benzyl-5-ethyl-2-piperidone (**5b**);[8] (±)-1-benzyl-2-oxo-4-piperidineacetic acid (**5c**);[8] (±)-*trans*-1-benzyl-5-ethyl-2-oxo-4-piperidineacetic acid (**7**);[5,9] (4*S*,5*R*)-(−)-1-(2-benzyloxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic acid [(−)-**9**].[4b]

Alkaline Hydrolysis of the Lactams 5a,b,c and 7——The procedure employed for **5a** will be described below in detail. The other lactams were treated similarly, and the results are summarized in Table I and in the text.

The substrate **5a** was dissolved in 2.5 N solution of KOH in 40% (w/w) aqueous EtOH at 0.2 M concentration, and 20-ml aliquots of the solution were placed in flasks and heated under reflux in an oil bath kept at 120 °C. At intervals the reaction was quenched by removing and cooling the flasks. The cooled solution was then concentrated *in vacuo*, H_2O (20 ml) was added to the residue, and the resulting aqueous mixture was extracted with four 20-ml portions of $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 (8 g) and concentrated *in vacuo*. The residual oil (**5a**) was weighed and identified by comparison of the infrared (IR) spectrum and thin-layer chromatographic (TLC) behavior [alumina, AcOEt–hexane (2 : 1, v/v)] with those of authentic **5a**. A blank experiment showed that the recovery of **5a** was 96%. On the other hand, the aqueous layer separated from the above $CHCl_3$ layer was made acid to Congo red with 10% aqueous HCl and concentrated *in vacuo* to leave a mixture of **4a** and KCl. The mixture was then shaken with a slight excess of benzoyl chloride and dilute aqueous KOH under ice-cooling for 10 min. The reaction mixture was filtered in order to remove insoluble material, and the filtrate was made acid to Congo red with 10% aqueous HCl. The colorless solid that resulted was filtered off, washed with a little H_2O, and recrystallized from 50% (v/v) aqueous EtOH to give 5-(*N*-benzylbenzamido)valeric acid as colorless needles, mp

124.5—125.5 °C (lit.[7] mp 124—125 °C), which were identical (by mixture melting point test and comparison of the IR spectrum and TLC behavior) with an authentic sample.[7] The reverse experiments with **6a**, generated *in situ* from **4a** and 1 N aqueous KOH, were also run in a similar manner.

In the case of **5b**, the hydrolyzed product **6b** was tosylated according to the reported procedure,[8] and the resulting *N*-tosyl derivative, mp 104—106 °C (lit.[8] mp 102—103 °C), was identical (by comparison of the IR spectrum and TLC behavior) with authentic 5-(*N*-benzyl-*p*-toluenesulfonamido)-4-ethylvaleric acid.[8] The reverse experiments with **6b**, generated *in situ* from crude **4b**[8] and 1 N aqueous KOH, were also conducted as described above for **6a**.

In the case of **5c**, 10 N aqueous KOH and the potassium salt **5d**, generated *in situ* from **5c** and an equimolar amount of 1 N aqueous KOH, were dissolved in aqueous EtOH to prepare 0.2 M solution of **5d** in 40% (w/w) aqueous EtOH containing KOH at 2.5 N concentration. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in H_2O. The aqueous solution was made acid to Congo red with 10% aqueous HCl and extracted with $CHCl_3$ to recover the unchanged lactam acid **5c**. The hydrolyzed product **6d** was isolated in the form of the hydrochloride **4c**·H_2O, mp 97—98 °C (lit.[8] mp 100—101 °C), which was identical (by comparison of the IR spectrum) with authentic 3-(2-benzylaminoethyl)glutaric acid hydrochloride monohydrate.[8]

The alkaline hydrolysis of **7** was achieved as described above for **5c**, and the ratios of the *cis* to the *trans* isomers in the recovered lactam fractions were determined by the previously reported ^{13}C-FT-NMR spectroscopic method.[1,4a,b,5,6]

Conversion of (−)-9 into (+)-13——The *cis*-lactam acid (−)-**9**[4b] was dissolved in an equimolar amount of 1 N aqueous KOH, and the resulting aqueous solution and 10 N aqueous KOH were dissolved in aqueous EtOH to obtain 0.2 M solution of the potassium salt of (−)-**9** in 40% (w/w) aqueous EtOH containing KOH at 2.5 N concentration. A portion (4.5 ml) of the solution was heated under reflux in an oil bath kept at 120 °C for 96 h. The reaction mixture was concentrated *in vacuo* to leave a colorless, thick oil, which was dissolved in H_2O (10 ml). The aqueous solution was made acid to Congo red with 10% aqueous HCl and extracted with four 20-ml portions of $CHCl_3$. The $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to leave **11** (390 mg, 95%) as a colorless solid, which was found to be a 49 : 51 mixture of the *cis* and the *trans* isomers on quantitative analysis using the previously reported ^{13}C-NMR spectroscopic method.[1] A portion (341 mg, 0.749 mmol) of the stereoisomeric mixture was dissolved in EtOH (6 ml), and the solution was hydrogenated over 10% Pd–C (80 mg) at atmospheric pressure and room temperature for 4 h. Removal of the catalyst by filtration and concentration of the filtrate left **12** (269 mg, 98%) as a colorless oil. The oil was dissolved in a little AcOEt and the AcOEt solution was kept in a refrigerator. The crystals that resulted were filtered off and dried to give crude (+)-**13** (103 mg, 38%), mp 147—152 °C. Recrystallization from AcOEt furnished a pure sample as colorless prisms, mp 153—155 °C; $[\alpha]_D^{30}$ +86.0° (c=1.01, EtOH) [lit.[4b] mp 154—155 °C; $[\alpha]_D^{15}$ +86.5° (c=1.00, EtOH)]. This sample was identical (by mixture melting point test and comparison of IR, ^{1}H-NMR, and ^{13}C-NMR spectra as well as TLC behavior) with authentic (4*R*,5*R*)-(+)-1-(2-hydroxy-3,4-dimethoxyphenethyl)-5-ethyl-2-oxo-4-piperidineacetic acid.[4b]

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