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Lactams. III.[1] Acid Hydrolysis of 1-Benzylhexahydro-2*H*-azepin-2-one

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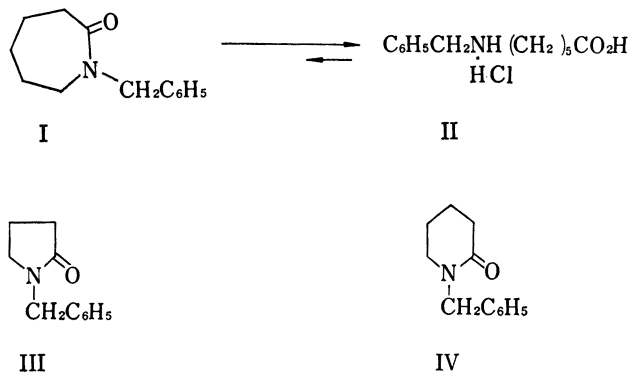
The previous papers[1,3] in this series have demonstrated the attainment of equilibrium between a lactam and the corresponding ω-amino acid hydrochloride in the hydrolysis of the former in boiling hydrochloric acid, and also discussed the effect of substituents and ring-size on the equilibrium. We have extended the hydrolysis study to include 1-benzylhexahydro-2*H*-azepin-2-one (I), a simple 7-membered lactam, in order to make a comparison with the hydrolysis of the 5-[1] and 6-membered lactams.[3]



I II

III IV

Chart 1

Lactam I was prepared by the method previously described,[4] and subjected to hydrolysis in boiling 6.04N hydrochloric acid. The progress of the reaction was followed by measuring the amount of the unaltered lactam in the same way as reported[3] previously. As shown in Fig. 1, the hydrolysis was so slow that it was unable to be complete within 72 hr. Since the percentage of hydrolysis obtained by extrapolation to infinite time is estimated at almost 100%, the equilibrium between I and 6-benzylaminohexanoic acid hydrochloride (II) must lie almost completely

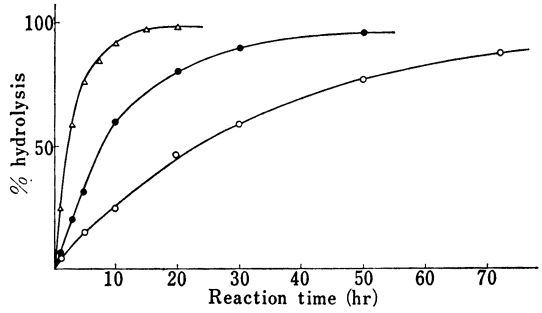


Fig. 1. Rate of Hydrolysis of 0.528M N-Benzyllactams in Boiling 6.04N HCl

—○—: 1-benzylhexahydro-2*H*-azepin-2-one (I)
—●—: 1-benzyl-2-pyrrolidinone (III)
—△—: 1-benzyl-2-piperidone (IV)

1) Part II: T. Fujii, S. Yoshifuji, and A. Tamai, *Chem. Pharm. Bull.* (Tokyo), **19**, 369 (1971).
2) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
3) T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970).
4) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

on the side of II, even if it exists. This was also indicated by the reverse experiment with II under the identical reaction condition; formation of lactam I was virtually nothing.

Fig. 1 also illustrates the rate of hydrolysis of 1-benzyl-2-pyrrolidinone (III) and 1-benzyl-2-piperidone (IV) obtained in the previous experiments.[1,3] In their hydrolysis study of N-methylated lactams, Bonetskaya, *et al.*[5] have obtained the rate order 6-> 7-> 5-> 8-membered lactam. In our cases, however, comparison of the initial rates suggests the order 6-> 5-> 7-membered lactam. Among the three models, the 5-membered lactam (III) seems to be the one that causes the lactam–ω-amino acid equilibrium to shift to the left farthest.

Experimental[6]

1-Benzylhexahydro-2*H*-azepin-2-one (I)——This was prepared by the reported method,[4] mp 56°; UV λ_{max} mμ (ε): 252.5 (174), 258.5 (207), 264.5 (155); IR ν_{max}^{KBr} cm^{-1}: 1633 (lactam), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1633 (lactam); NMR ($CDCl_3$) τ: 8.38 (6H, m, b, $H_{(4)}$,s, $H_{(5)}$,s, and $H_{(6)}$,s), 7.43 (2H, m, $H_{(3)}$,s), 6.75 (2H, m, $H_{(7)}$,s), 5.43 (2H, s, $NCH_2C_6H_5$), 2.75 (5H, s, C_6H_5).

Hydrolysis of Lactam I——The progress of hydrolysis of I in boiling 6.04N HCl at 0.528M concentration was followed in the same manner as reported[3] previously. The results are shown in Fig. 1.

6-Benzylaminohexanoic Acid Hydrochloride (II)——A mixture of I (1.07 g) and 20% aq. HCl (10 ml) was refluxed for 50 hr. The solution was evaporated *in vacuo* and H_2O (20 ml) was added to the residue. The mixture was extracted with $CHCl_3$ in order to remove the unchanged I. The aq. layer separated from the $CHCl_3$ layer was evaporated *in vacuo* to leave a solid, which was dried. The solid was dissolved in a small amount of warm EtOH and then hot CCl_4 was added. After having been cooled, the mixture separated colorless scales of mp 147.5—148.5°. Repeated recrystallizations in the same way gave an analytical sample, mp 148—149°. *Anal.* Calcd. for $C_{13}H_{20}O_2NCl$: C, 60.66; H, 7.82; N, 5.44. Found: C, 60.64; H, 7.90; N, 5.57.

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5) A.K. Bonetskaya, N.F. Erofeeva, S.M. Skuratov, and R.S. Muromova, *Izv. Vysshikh Uchebn. Zavedenii, Khim. i Khim. Tekhnol.*, **4**, 74 (1961) [*Chem. Abstr.*, **55**, 15071*h* (1961)].

6) All melting points are corrected. The UV spectrum was determined with a Hitachi EPS-2U spectrophotometer in 95% aq. EtOH. The IR spectra were recorded on a JASCO-DS-402G spectrophotometer and the NMR spectrum was obtained with a JEOL-JNM-C-60H spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, m=multiplet, s=singlet.