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Takehisa Kunieda, Kenji Koga, and Shun-ichi Yamada : Studies on Optically Active Amino Acids. XIII.[*1] Racemization of N-Benzoylanilides of Optically Active Proline and Pipecolic Acid.

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In part XII[1] of this series, the present authors reported the influence of the ring size on the behavior for racemization of bicyclic α-amino-ketones having the asymmetric carbon atom adjacent to the bridge-head nitrogen and carbonyl group. The present investigation was undertaken to examine the effect of ring size on the rate of racemization of monocyclic α-amino acid derivatives. It is generally accepted that N-acylated and carboxyl-substituted α-amino acids could be racemized more easily under either basic or acidic conditions than the corresponding unsubstituted[2], and Bovarnick, *et al.*[3] reported that N-benzoylanilides of α-amino acids were racemized easily under mild alkaline conditions. Recently, the systematic investigation was undataken by Matsuo, *et al.*[4] on the rate of racemization of various derivatives of acyclic α-amino acids.

In the present work, N-benzoylanilides of L-proline and D-pipecolic acid were chosen as substrates to measure the rate of racemization.

(−)-1-Benzoyl-2-pyrrolidinecarboxanilide(I), m.p. 185~186°, $[\alpha]_D$ −116.5° (EtOH), was prepared from N-benzoyl-L-proline by both the DCC method and the mixed carboxylic-carbonic anhydride method in 59% and 63% yield, respectively. (+)-1-Benzoyl-2-piperidinecarboxanilide (II), m.p. 167~169°, $[\alpha]_D$ +27.2° (EtOH), was similarly synthesized from N-benzoyl-D-pipecolic acid by the DCC method in 42% yield, while the corresponding racemate of II was obtained by the mixed anhydride method.

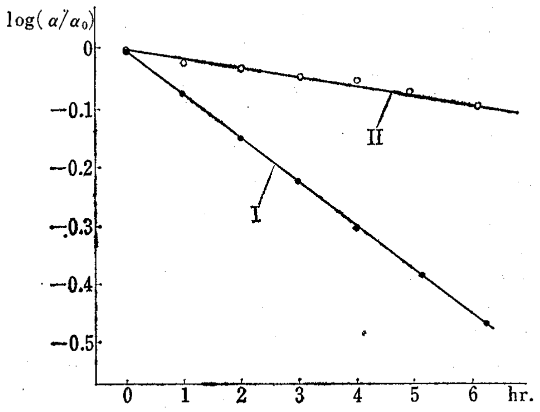

Fig. 1. Racemization of 1-Benzoyl-2-pyrrolidinecarboxanilide (I) and 1-Benzoyl-2-piperidinecarboxanilide (II) in NaOEt-DMSO at 40°

The rate of racemization was measured polarimetrically in DMSO solution at 40° ±0.5°, using about 3 fold moles of sodium ethoxide as a base. In each case, the logarithms of the term α/α_0, where α_0 and α are the initial rotation and the rotation after time t, respectively, at appropriate intervals of time were plotted against time t to draw a good linear line as shown in Fig. 1, from which pseudo first order rate constant (k) and the half-time ($t_{1/2}$) for racemization were calculated. The results are given in Table I.

[*1] Part XII : This Bulletin, **15**, 337 (1967).

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Table I. Data for Racemization of N-Benzoylanilides of Proline and Pipecolic Acid (at 40°, in NaOEt-DMSO)

Compounds	Pseudo first order rate constants (k), min^{-1}	Half-times ($t_{1/2}$), min.
I	2.88×10^{-3}	240
II	5.12×10^{-4}	1350

The five-membered ring compound I was found to be racemized as fast as six times than the six-membered ring compound II under the condition. That the hybridization from sp^3 to sp^2 at the asymmetric carbon atom in I might release a considerable conformational strain caused by the bond oppositions at the transition state of racemization could well account for the above results, since this relief might presumably overweigh the angular strain at the asymmetric carbon atom involved in the change from sp^3 to sp^2.

Experimental[*3]

(−)-1-Benzoyl-2-pyrrolidinecarboxanilide (I)——a) To a solution of 2.1 g. (0.01 mole) of N-benzoyl-L-proline[5] and 0.93 g. (0.01 mole) of aniline in 45 ml. of CH_2Cl_2 was added 2.0 g. (0.01 mole) of DCC and the mixture was stirred at room temperature for 3.5 hr. Then the precipitate deposited was filtered off, the filtrate was washed with aq. $NaHCO_3$, dried and evaporated *in vacuo*. Recrystallization from EtOH afforded 1.7 g. (58.5%) as colorless prisms, m.p. 185~186°, $[\alpha]_D^{14}$ −115.6° (c=1.6, EtOH). IR $\nu_{\max}^{KBr}$ cm^{-1}: 3270 (NH), 1698 (CONH), 1615 (CON), 1555 (Amide II). *Anal.* Calcd. for $C_{18}H_{18}O_2N_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.18; H, 6.10; N, 9.72.

b) A mixture of 6.57 g. (0.03 mole) of N-benzoyl-L-proline[5] and 3.03 g. (0.03 mole) of Et_3N in 120 ml. of abs. toluene was cooled to −7~−5° and 3.26 g. (0.03 mole) of ethyl chloroformate was added dropwise at the same temperature. After the complete addition, the mixture was kept at −5° for 25 min. To this solution was added 2.8 g. (0.03 mole) of aniline and the mixture was allowed to stand at room temperature overnight. The precipitate was separated by filtration and the filtrate was washed with dil. HCl and aq. $NaHCO_3$. After drying and removal of the solvent, the resulting solid was recrystallized from EtOH to yield 5.5 g. (62.5%) of colorless prisms, m.p. 185~186°, $[\alpha]_D^{13}$ −116.5° (c=1.6, EtOH). The IR spectrum (KBr) was identical with that of the compound prepared above DCC method.

(+)-1-Benzoyl-2-piperidinecarboxanilide (II)——a) To a solution of 2.0 g. (0.0086 mole) of N-benzoyl-D-pipecolic acid,[1,6] $[\alpha]_D^{18}$ +55.8° (c=1.04, EtOH), and 0.8 g. (0.0086 mole) of aniline in 40 ml. of CH_2Cl_2 was added 1.8 g. (0.0088 mole) of DCC and the mixture was stirred at room temperature for 3 hr. In the same way as (−)-I, 1.1 g. (42%) of (+)-II was obtained as colorless prisms, m.p. 167~169°, $[\alpha]_D^{12}$ +27.2° (c=2.03, EtOH), $[\alpha]_D^{12}$ +60.0° (c=2.68, benzene). IR $\nu_{\max}^{KBr}$ cm^{-1}: 3275 (NH), 1688 (CONH), 1620 (CON), 1540 (Amide II). *Anal.* Calcd. for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.12; H, 6.63; N, 9.11.

b) The mixed anhydride method using 1.4 g. (0.013 mole) of ethyl chloroformate was carried out to 3 g. (0.013 mole) of N-benzoyl-D-pipecolic acid in the same manner as described above, and the product was roughly chromatographed on alumina and recrystallized from EtOH. Only the racemate of II was isolated, weighing 0.9 g. (23%), m.p. 167~169°. The IR spectrum (KBr) was identical with that of (+)-II. No racemization of (+)-II was observed by chromatography on Al_2O_3.

Measurements of the Rate Constant for Racemization——In 25 ml. of the solvent containing 0.18 g. (0.0078 atom) of metallic sodium, 5.5 g. of abs. EtOH and 50 g. of DMSO (distilled over CaH_2) was dissolved about 0.4 g. (0.0013 mole) each of the sample, (−)-I and (+)-II. The solution was divided into several parts evenly, every part was sealed and kept at 40°±0.5. The loss of optical activity was followed polarimetrically at an interval of 1 hr. The graph in Fig. 1 was obtained by plotting the logarithms of α/α_0, where α_0 is initial rotaion and α is rotation after time t, against time t, indicating pseudo first order reaction. The rate constant (k) and half-period ($t_{1/2}$) for racemization were calculated from the equation, $kt=\ln \alpha_0/\alpha$.

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[*3] All melting points are uncorrected.

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