Takehisa Kunieda, Kenji Koga, and Shun-ichi Yamada : Studies on
Optically Active Amino Acids. XIll, Racemization of
N-Benzoylanilides of Optically Active
Proline and Pipelic Acid.

(Faculty of Pharmaceutical Sciences, University of Tokyo**)

(Received July 4, 1966)

In part XIll of this series, the present authors reported the influence of the ring
size on the behavior for racemization of bicyclic \(\alpha\)-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 \(\alpha\)-amino acid derivatives. It is generally accepted that N-acylated and carboxyl-substituted \(\alpha\)-amino acids could be racemized more easily under either basic or acidic conditions than the corresponding unsubstituted, and Bovarnick, et al. reported that N-benzoylanilides of \(\alpha\)-amino acids were racemized easily under mild alkaline conditions. Recently, the systematic investigation was undated by Matsuo, et al. on the rate of racemization of various derivatives of acyclic \(\alpha\)-amino acids.

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

\((-\rangle-1\)-Benzoyl-2-pyrrolidinocarboxanilide(\(I\)), m.p. 185-186\(^\circ\), \([\alpha]_D -116.5^\circ\) (EtOH), was prepared from N-benzoyl-L-proline by both the DCC method and the mixed carboxyllic-carbonic anhydride method in 59\% and 63\% yield, respectively. \((+\rangle-1\)-Benzoyl-2-piperidinocarboxanilide(\(II\)), m.p. 167-169\(^\circ\), \([\alpha]_D +27.2^\circ\) (EtOH), was similarly synthesized from N-benzoyl-d-pipelic acid by the DCC method in 42\% yield, while the corresponding racemate of \(II\) was obtained by the mixed anhydride method.

The rate of racemization was measured polarimetrically in DMSO solution at 40\(^\circ\) ±0.5\(^\circ\), using about 3 fold moles of sodium ethoxide as a base. In each case, the logarithms of the term \(\alpha/\alpha_o\), where \(\alpha_o\) and \(\alpha\) 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 XIll: This Bulletin, 15, 337 (1967).
\(*2\) Hongo 7, Tokyo (四枝武久, 吉澤雅司, 山田俊一).
4) H. Matsuo, Y. Fujimoto, T. Tatsuno, K. Sato: The abstract of the 85th Annual Meeting of the
Table I. Data for Racemization of N-Benzoylanilides of Proline
and Pipelic Acid (at 40°, in NaOEt-DMSO)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Pseudo first order rate constants (k), min⁻¹</th>
<th>Half-times (t½), min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>2.88×10⁻³</td>
<td>240</td>
</tr>
<tr>
<td>II</td>
<td>5.12×10⁻⁴</td>
<td>1350</td>
</tr>
</tbody>
</table>

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 sp³ to sp² 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 outweigh the angular strain at the asymmetric carbon atom involved in the change from sp³ to sp².

Experimental

(−)-1-Benzoyl-2-pyrrolidinaceboxanilide (I) — a) To a solution of 2.1 g. (0.01 mole) of N-benzoyl-L-proline and 0.93 g. (0.01 mole) of aniline in 45 ml. of CH₂Cl₂ 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. NaHCO₃, dried and evaporated in vacuo. Recrystallization from EtOH afforded 1.74 g. (58.5%) as colorless prisms, m.p. 185~186°, [α]D¹₅ = 115.6° (c = 1.6, EtOH). IR νmax cm⁻¹: 3270 (NH), 1688 (CONH), 1615 (CON), 1555 (Amide II). Anal. Calcd. for C₁₆H₁₉O₂N₂: 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 and 3.03 g. (0.03 mole) of Et₂N 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. NaHCO₃. 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°, [α]D¹₅ = 116.5° (c = 1.6, EtOH). The IR spectrum (KBr) was identical with that of the compound prepared above DCC method.

(+)-1-Benzoyl-2-piperidinaceboxanilide (II) — a) To a solution of 2.0 g. (0.0086 mole) of N-benzoyl-L-pipelic acid,¹⁴ [α]D¹₅ = +55.8° (c = 1.04, EtOH), and 0.8 g. (0.0086 mole) of aniline in 40 ml. of CH₂Cl₂ 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°, [α]D¹₅ = +27.2° (c = 2.03, EtOH), [α]D¹₅ = +60.0° (c = 2.68, benzene). IR νmax cm⁻¹: 3275 (NH), 1688 (CONH), 1620 (CON), 1540 (Amide II). Anal. Calcd. for C₁₆H₁₉O₂N₂: 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-L-pipelic 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 Al₂O₃.

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 CaH₂) was dissolved about 0.4 g. (0.0013 mole) each of the sample, (−)-I and (−)-II. The solution was divided into several parts, every part was evenly spread 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 a/a₀, where a₀ is initial rotation and a is rotation after time t, against time t, indicating pseudo first order reaction. The rate constant (k) and half-period (t½) for racemization were calculated from the equation, k = ln a₀/a.

The authors are grateful to the members of the Central Analysis Room of this Faculty for microanalyses and measurement of IR spectra. A donation of L-proline from Ajinomoto Co., Ltd. is also gratefully acknowledged.

¹⁴ All melting points are uncorrected.