Baldwin Rules for Ring Closure – a Re-examination of the Concept*

V. K. Kansal and A. P. Bhaduri**
Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow-226001, India

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Primary Amines, 5,5-Diphenyl-γ-butyrolactone

The reaction of 5,5-diphenyl-γ-butyrolactone (3) with primary amines and ethyl γ-γ-diphenyl vinyl acetate with Aqu HBr in acetic acid served as examples for the exception to Baldwin rules for 5-exo-tet and 5-exo-trig ring closures. The structure of the reaction product of 3 with primary amines have been assigned on the basis of spectral data and conversion to γ-γ-diphenyl vinyl substituted acetamides, the authentic samples of which were prepared by an unambiguous route of synthesis.

Opportunity to examine the Baldwin rules for ring closure [1-2] was obtained during the course of our investigation on the synthesis of a few five membered heterocyclic systems. The results obtained are recorded in this communication.

The reaction of γ-butyrolactone with primary amines have been reported earlier to yield pyrrolidone derivatives [3-4]. In these reactions possibly 5-exo-tet ring closure yielded the five membered heterocycles. The reaction of 5,5-diphenyl-γ-butyrolactone (3), however, with 3,4-dimethoxyphenyl-ethylamine under various experimental conditions [3-4] failed to yield the desired pyrrolidone derivatives. The structure of this reaction product (9) was assigned on the basis of spectral data (Table I) and the conclusive evidence for the assigned structure (9) was obtained by dehydrating it with concentrated H2SO4 acid to 5, which gave superimposable IR and

Table I. Experimental data of 1-11.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Yield [%]</th>
<th>m.p.°C</th>
<th>Molecular formula</th>
<th>Spectroscopic data (PMR: ppm^a and IR: cm(^{-1}))</th>
<th>Elemental analyses (Calcd: Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>85</td>
<td>Oil</td>
<td>C(<em>{16})H(</em>{15})O(_{2}) (266.3)</td>
<td>PMR (CCl(<em>{4})): 1.13 (t, 3H, -CH(</em>{2})-CH(<em>{3})), 2.96 (d, 2H, J = 7 Hz, =CH-CH(</em>{2})), 3.69 (q, 2H, -CH(<em>{2})-CH(</em>{3})), 6.08 (t, 1H, =CH-CH(_{2})-) and 6.9-7.2 (m, 10H, Ar-H)</td>
<td>C: 81.17 C: 81.40 H: 6.81 H: 6.93</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>148</td>
<td>C(<em>{13})H(</em>{21})NO (279.4)</td>
<td>PMR (CCl(<em>{4})+ TFA): 1.05 (d, 6H, -CH-(CH(</em>{3}))(<em>{2})), 2.9 (d, 2H, J = 7 Hz, =CH-CH(</em>{2})), 4.0 (m, 1H, -CH-(CH(<em>{3}))(</em>{2})), 6.2 (t, 1H, =CH-CH(_{2})-) and 7.0-7.2 (m, 10H, Ar-H)</td>
<td>C: 81.68 C: 81.00 H: 7.58 H: 7.95 N: 5.01 N: 5.06</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>94-95</td>
<td>C(<em>{26})H(</em>{27})NO(_{3}) (401.5)</td>
<td>PMR (CDCl(<em>{3})): 2.66 (t, 2H, CH(</em>{2})Ph), 2.9 (d, 2H, J = 7 Hz, =CH-CH(<em>{2})), 3.33 (t, 2H, NH-CH(</em>{2})), 3.66 (s, 6H, OCH(<em>{3})), 6.1 (t, 1H, =CH CH(</em>{2})), 6.9-7.2 (m, 10H, Ar-H)</td>
<td>C: 76.19 C: 76.20 H: 6.84 H: 6.68 N: 3.41 N: 3.09</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>102–103</td>
<td>C(<em>{26})H(</em>{25})NO (355.5)</td>
<td>PMR (CDCl(<em>{3})): 2.22 (s, 3H, Ar-CH(</em>{3})), 2.8 (t, 2H, Ph-CH(<em>{2})), 3.04 (d, 2H, =CH-CH(</em>{2})), 3.3 (t, 2H, -NH-CH(<em>{3})), 6.14 (t, 1H, =CH CH(</em>{2})) and 6.8-7.5 (m, 14H, Ar-H)</td>
<td>C: 84.47 C: 84.02 H: 7.09 H: 7.04 N: 3.94 N: 3.79</td>
</tr>
</tbody>
</table>

* C.D.R.I. Communication No. 2737. ** Reprint requests to A. P. Bhaduri.

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Table I (continued).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Yield</th>
<th>m.p.</th>
<th>Molecular formula</th>
<th>Spectroscopic data (PMR: ppmz and IR: cm⁻¹)</th>
<th>Elemental analyses (Calcd: Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>70</td>
<td>141-142</td>
<td>C_{23}H_{31}NO</td>
<td>PMR (CDCl₃): 3.0 (d, 2H, =CH CH₂), 4.28 (d, 2H, J = 6 Hz, NH CH₂), 6.17 (t, 1H, -CH CH₂) and 6.9-7.3 (m, 15H, Ar-H) &lt;br&gt;IR (KBr): 1640 (&gt;C = O) and 3320 (NH-H)</td>
<td>C: 84.37 C: 84.12 H: 6.46 H: 6.40 N: 4.28 N: 4.46</td>
</tr>
<tr>
<td>8</td>
<td>85</td>
<td>148</td>
<td>C_{12}H_{22}NO₂</td>
<td>PMR (CDCl₃ + TFA): 1.0 (d, 6H, -CH(CH₃)₂), 2.83 (t, 4H, -CO-CH₃ CH₂-C-), 3.95 (m, 1H, =CH CH₂ and 6.8-7.1 (m, 10H, Ar-H) &lt;br&gt;IR (KBr): 1640 (&gt;C = O) and 3350 (NH and OH)</td>
<td>C: 76.74 C: 76.50 H: 7.80 H: 7.74 N: 4.71 N: 4.58</td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td>148-149</td>
<td>C_{26}H_{29}NO₄</td>
<td>PMR (CDCl₃): 2.04 (t, 2H, -CH(CH₃)₂), 2.54 (q, 4H, CH₂CO and CH₂-C-Ph), 3.26 (q, 2H, NH-CH₂), 3.7 (s, 6H, (OMe)₂), 4.6 (s, 1H, C-OH), 5.7 (t, 1H, NH), 6.4-6.7 (m, 3H, Ar-H) and 7-7.35 (m, 10H, Ar-H) &lt;br&gt;IR (KBr): 1635 (&gt;C = O) and 3330 (NH and OH)</td>
<td>C: 74.44 C: 74.30 H: 6.97 H: 7.40 N: 3.44</td>
</tr>
<tr>
<td>10</td>
<td>86</td>
<td>104</td>
<td>C_{26}H_{27}NO₂</td>
<td>PMR (CDCl₃): 1.95 (t, 2H, -CH₂-C-), 2.15 (s, 3H, -CH₃), 2.46 (q, 4H, CH₂CO and CH₂Ar)², 3.18 (q, 2H, NH-CH₂)², 4.6 (s, 1H, -OH), 5.66 (t, 1H, NH), 6.85 (s, 4H, Ar-H) and 6.9-7.3 (m, 10H, Ar-H) &lt;br&gt;IR (KBr): 1635 (C=O) and 3300 (NH and OH)</td>
<td>C: 80.40 C: 80.70 H: 7.29 H: 7.02 N: 3.75 N: 3.74</td>
</tr>
<tr>
<td>11</td>
<td>80</td>
<td>132</td>
<td>C_{26}H_{23}NO₂</td>
<td>PMR (CDCl₃): 2.12 (t, 2H, CH₂-C-), 2.55 (t, 2H, CH₂CO), 4.2 (d, 2H, J = 5 Hz, CH₂Ph), 5.85 (t, 2H, NH) and 6.9-7.4 (m, 15H, Ar-H) &lt;br&gt;IR (KBr): 1635 (&gt;C = O) and 3300 (NH and OH)</td>
<td>C: 79.97 C: 79.80 H: 6.71 H: 6.40 N: 4.01 N: 4.00</td>
</tr>
</tbody>
</table>

* All melting points are uncorrected; b analyses as hemihydrate; c false quartets formed due to merging of two triplets; d the NMR spectra were recorded on Perkin-Elmer (R-32) NMR spectrometer (90 MHz) using TMS as internal standard.

PMR spectra with an authentic sample prepared by reaction γ,γ-diphenyl vinyl acetyl chloride with 3,4-dimethoxy phenylethylamine. Similar course of reaction with other primary amines indicated the general behaviour of 3 towards ring closure and precisely this was the reason which led to the identification of each reaction product in the same manner as has been described for the assignment of structure 9. Keeping in view of the earlier observation [3-4], the inability of 3 to undergo favoured 5-exo-tet ring closure during its reaction with primary amines, is an exception to the Baldwin rule. However, the validity of the postulated disfavoured 5-endo-trig ring closure, examined on the basis of attempted cyclisation of 5 to the corresponding pyrrolidone derivative under various experimental conditions was found to be true. Yet another exception to the Baldwin rule for ring closure was observed during the cyclisation of γ,γ-diphenyl vinyl acetic acid and its ethyl ester to
the lactone (3). Reaction of γ,γ-diphenyl vinyl acetic acid with Aq. HBr in acetic acid gave 3 and its formation could be explained on the basis of addition of a molecule of water followed by favoured 5-exo-trig cyclisation. Attempt to cyclise γ,γ-diphenyl vinyl acetic acid with Aq. ethanol and conc. HCl yielded ethyl γ,γ-diphenyl vinyl acetate (2). Reaction of this compound with Aq. HBr in ACOH acid failed to yield 3. This observation was interesting because 2 could also undergo the addition of water followed by 5-exo-trig cyclisation. The dissimilar behaviour of the acid (1) and the ester (2) furnished the exception to the Baldwin rule.

A rational explanation for the inability of 5,5-diphenyl γ-bytyrolactone to yield the required pyrrolidone derivatives was obtained from the molecular model which indicated a steric hinderance for the correct trajectory of the nucleophilic attack. At present no rational explanation for the dissimilar behaviour of 1 and 2 towards 5-exo-trig cyclisation can be furnished.

**Experimental**

1. **Reaction of γ,γ-diphenyl vinyl acetic acid (1)** with HBr in ACOH acid

   A solution of γ,γ-diphenyl vinyl acetic acid [5] (1) (.01 mole), Aq. HBr (48%; 4 ml) and water (1 ml) in glacial acetic acid (12 ml) was refluxed for 2 h under stirring. The reaction was continued at room temperature (30–35 °C) for 16 h, poured into ice and extracted with ether. The organic layer was washed with a solution of K₂CO₃ (5%) followed by water and was dried over anhydrous sodium sulphate. Removal of the ether and the recrystallisation of the residue with a mixture of Benzene and Hexane gave 3. 1.8 g (75%); m.p. 88–89 °C (Lit. [5] m.p. 90–91 °C).

2. **Ethyl γ,γ-diphenyl vinyl acetate**
   a) A solution of 1 (.01 mole) in ethanol (20 ml) and conc. HCl (5 ml) was stirred at room temperature for 16 h. The solvent was removed and the residue was extracted with ether. The usual work up of the organic layer yielded 2.
   b) 3 also gave 2 in the same reaction conditions.

3. **4,4-Diphenyl-4-hydroxy-substituted-butyramides (8–11)**

   A solution of 3 (.01 mole) and appropriate primary amine (.012 mole) in methanol (30 ml) was heated at 180 °C in a steel bomb for 24 h, after cooling the solvent was removed from the reaction mixture and the residue extracted with ethyl acetate. The usual work up of the organic layer after washing HCl (10%) yielded the desired 4,4-diphenyl, 4-hydroxy-substituted butyramides (8–11).

4. **γ,γ-Diphenyl substituted vinyl acetamides (4–7)**

   To a solution of 1 (.01 mole) in dry benzene (20 ml) was added slowly SOCl₂ (.015 mole) dissolved in dry benzene (15 ml) and was stirred at room temperature for 35 min. The solvent was removed under vacuum and the residue was redissolved in dry benzene. To this was added continuously the appropriate amine (.02 mole) dissolved in dry benzene and the reaction mixture was stirred at room temp. for 2 h. The organic layer was then washed with HCl (10%), followed by NaHCO₃ solution (10%) and the usual work up yielded the desired compound which was recrystallised from a mixture of benzene and hexane.

5. **Dehydration of 4,4-diphenyl-4-hydroxy-substituted butyramide**

   Appropriate 4,4-diphenyl-4-hydroxy substituted butyramide (100 mg) dissolved in ethanol (2 ml) and conc. H₂SO₄ (.4 ml) was stirred for 6 h at room temperature. The mixture was then poured into ice, extracted with ether and washed with water. The usual work up of the organic layer furnished the desired γ,γ-diphenyl vinyl acetamides (4–7).

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