Intramolecular Cyclocondensation of 4- and 5-Oxo-carboxylic Acids to Five- and Six-Membered Ring Systems

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In connection with earlier studies concerning the preparation of reactive intermediates for the synthesis of octahydropyridine alkaloids, we investigated the cyclization of the dicarboxylic acids 2 and their monoamides 3.

Compounds 23 and 3 were prepared from N,N-dimethyl-3-acyl-3-aryl-6-nitrohexanamides (1) by alkaline or acidic hydrolysis, respectively. Compounds 1 were in turn obtained by cyanoethylation of the previously described N,N-dimethyl-3-aryl-4-oxopentanamides (3-arylevinamides).

Compounds 2 may be expected to undergo the following types of cyclization reactions in which they react as 4- or 5-oxaalkanoic acids:

(a) Enol lactonization of the free acids or their reactive derivatives (anhydrides, acid chlorides);
(b) Intramolecular acylation of the C-methyl group under the conditions of a Dieckmann condensation;
(c) Intramolecular Friedel-Crafts acylation.

We studied the cyclization behaviour of the acids 2 using 3-aryl-4-oxopentanoic acids (4), 4-aryl-5-oxoheptanoic acids (5), and the ethyl esters thereof (6, 9) as model compounds.

The formation of other possible cyclization products from 4 or 5 such as cyclopentanones or indanes was not observed. On the other hand, the homologous acids 8 undergo exclusive cyclocondensation to 4-acetyl-1-tetralones (10) under the same conditions. With acetic anhydride, however, cyclization does not occur, the only isolable product being the anhydride of 8c. Contrary to 5, the ethyl ester 9 may be cyclized to the 4-phenyl-1,3-cyclohexanediones 11 the structure of which was assigned on the basis of the I.R. and 1H-N.M.R. spectra.

Application of the acid-catalyzed cyclization to the dicarboxylic acids 2 and 19 yields analogous results. The cyclization of 2c using sulfuric acid affords the 1-tetralone 13 whereas the analogous treatment of 2c with polyphosphoric acid leads to a not yet identified product the microanalysis and mass spectrum of which indicate loss of 1 mol water as compared to 13. Basic hydrolysis of the unknown product affords 13; this fact suggests linkage of the side chains via lactonization. Compound 2a is cyclized in sulfuric acid to give the cyclohexanone 18a; a similar reaction, i.e., cyclization of 19a to the homologous 20a, has already been reported. Treatment of 2n with polyphosphoric acid directly affords the unsaturated lactone 12a; however, when the amount of polyphosphoric acid used is not sufficient to bring about complete cyclization of 2a, the monocyclic compound 18a is obtained. Compounds 12 and 21 may be obtained from 18 and 20, respectively, using acetic anhydride or thionyl chloride.

Compound 18 may also be prepared from 16 or 17 by hy-
The dione structure of 16 and 17 can be excluded on the basis of the I.R. and 1H-N.M.R. spectra as well as from the conversion of 16 and 17 to 12.

As expected, tetrabones are the main products obtained from the reaction of o- cresol with the ketones 1a,c.5

whereas the tricyclic compound 23 is formed with demethylation of one methoxy group when polyphosphoric acid is used as the condensing agent. Treatment of 19a with polyphosphoric acid affords the spiro triketone 24.
<table>
<thead>
<tr>
<th>Product from Educt</th>
<th>Cond.</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>Molecular formula*</th>
<th>I.R. (KBr) ν [cm⁻¹]</th>
<th>δ [ppm]</th>
<th>Other Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a Na</td>
<td>63</td>
<td>113</td>
<td>C₁₁H₁₆O₅ (188.2)</td>
<td>1605; 1598</td>
<td>5.65 [s, 1 H (75%), H; 9.83 [s, 1 H (75%), CH₃ CH₃]; 9.83 [s, 1 H (75%), CH₃ OH]; 75% enolization]</td>
<td>5.56 [s, 1 H (75%), = CH]</td>
<td></td>
</tr>
<tr>
<td>11c Na</td>
<td>58</td>
<td>125–126</td>
<td>C₁₁H₁₆O₅ (306.3)</td>
<td>1705; 1670</td>
<td>2.15 (s, 3 H, COCH₃); 7.32, 7.49 (s, 2 Hbenz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12c H₂SO₄</td>
<td>19</td>
<td>126</td>
<td>C₁₁H₁₆O₅ (320.3)</td>
<td>1710; 1676</td>
<td>2.08 (s, 3 H, CO–CH₃); 6.60, 7.63 (s, 2 Hbenz)</td>
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<td></td>
</tr>
<tr>
<td>10a PPA (+ hydrolysis)</td>
<td>24</td>
<td>198</td>
<td>C₁₁H₁₆O₅ (228.2)</td>
<td>1830; 1660</td>
<td>3.04 (s, 2 H, CH₂ CO); 6.00 (s, 1 H, = CH)</td>
<td>M.S.: m/e = 228.1 (M⁺, 100%)</td>
<td>M.S.: m/e = 228.1 (M⁺, 100%); 57 (100)</td>
</tr>
<tr>
<td>12a PPA</td>
<td>47</td>
<td>92–93</td>
<td>C₁₁H₁₆O₅ (228.2)</td>
<td>1830; 1660</td>
<td>3.04 (s, 2 H, CH₂ CO); 6.00 (s, 1 H, = CH)</td>
<td>M.S.: m/e = 228.1 (M⁺, 100%); 57 (100)</td>
<td></td>
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<tr>
<td>12c AC₂O</td>
<td>51</td>
<td>134</td>
<td>C₁₁H₁₆O₅ (208.3)</td>
<td>1813; 1675</td>
<td>5.53 (s, 1 H, = CH)</td>
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<td></td>
</tr>
<tr>
<td>11a Na</td>
<td>73</td>
<td>148</td>
<td>C₁₁H₁₆O₅ (274.3)</td>
<td>1728</td>
<td>5.53 (s, 1 H, = CH)</td>
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<td></td>
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<tr>
<td>12c H₂SO₄</td>
<td>52</td>
<td>170–171</td>
<td>C₁₁H₁₆O₅ (246.3)</td>
<td>3408; 1690</td>
<td>(DMSO-d₆/TMS): 2.69 (ABq, 2H, CH₃ CO); δ₁ = 2.62, δ₂ = 2.75, J = 16.4 Hz</td>
<td>M.S.: m/e = 246.1 (M⁺, 100%)</td>
<td></td>
</tr>
<tr>
<td>12c PPA (1/2 amount)</td>
<td>75</td>
<td>200–201</td>
<td>C₁₁H₁₆O₅ (306.3)</td>
<td>1700</td>
<td>(DMSO-d₆/TMS): 2.69 (ABq, 2H, CH₃ CO); δ₁ = 2.62, δ₂ = 2.75, J = 16.4 Hz</td>
<td>M.S.: m/e = 246.1 (M⁺, 100%)</td>
<td></td>
</tr>
<tr>
<td>12c hydrolysis</td>
<td>85</td>
<td>54</td>
<td>C₁₁H₁₆O₅ (306.3)</td>
<td>1700</td>
<td>(DMSO-d₆/TMS): 2.69 (ABq, 2H, CH₃ CO); δ₁ = 2.62, δ₂ = 2.75, J = 16.4 Hz</td>
<td>M.S.: m/e = 246.1 (M⁺, 100%)</td>
<td></td>
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<tr>
<td>23 PPA</td>
<td>42</td>
<td>169–170</td>
<td>C₁₁H₁₆O₅ (288.3)</td>
<td>1710; 1674; 1648</td>
<td>2.21 (s, 3 H, CO–CH₃); 3.93 (s, 3 H, O–CH₃); 13.56 (s, 1 H, = OH)</td>
<td>strong intramolecular hydrogen bond (νOH band absent), forms colored Fe chelates</td>
<td></td>
</tr>
<tr>
<td>24 PPA</td>
<td>28</td>
<td>197</td>
<td>C₁₁H₁₆O₅ (242.3)</td>
<td>1690; 1618; 1598</td>
<td>5.48 (s, 1 H, = CH)</td>
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</tbody>
</table>

* The microanalyses were in good agreement with the calculated values: C, ±0.31; H, ±0.19; N, ±0.18.

** Purified by column chromatography on silica gel using benzene/ethyl acetate (3/1) as eluent.

### Cyclization Reactions in Polyphosphoric Acid or Sulfuric Acid; General Procedure:
A stirred suspension of the carboxylic acid (0.1 mol) in polyphosphoric acid (PPA; 35 g per 1 carboxy group) or 65% sulfuric acid (160 ml per 1 carboxy group) is heated at 100 °C for 2 h. When PPA is used the mixture is decomposed by the addition of water (100 ml for 35 g PPA); when sulfuric acid is used the mixture is poured into water (800 ml). Crystallization occurs spontaneously. The product is isolated by suction and recrystallized. Alternatively, the product is extracted from the aqueous-organic two-phase mixture using chloroform (3 × 50 ml), the extract is washed with saturated sodium hydrogen carbonate solution (30 ml) and then water (50 ml), and the solvent is evaporated; the residue is recrystallized from an appropriate solvent (isopropanol, ethanol, ethyl acetate, diisopropyl ether).

### Cyclization Reactions in Acetic Anhydride or Thionyl Chloride; General Procedure:
The carboxylic acid is dissolved in excess acetic anhydride or thionyl chloride and the solution refluxed for 2 h. The solvent is then evaporated and the residue recrystallized from appropriate solvents.

### Cyclization of Carboxylic Esters using Sodium in Toluene; General Procedure:
A solution of the ester (0.1 mol) in dry toluene (50 ml) is added to a suspension of sodium (2.3 g, 0.1 mol) in toluene (80 ml) containing absolute ethanol (0.5 ml). The mixture is refluxed for 3 h and the solid sodium salt is filtered off. The salt is dissolved in water (50 ml), the solution acidified with mineral acid to pH 2, and extracted with chloroform (3 × 20 ml). The solvent is evaporated and the residual product is recrystallized from isopropanol or ethanol.
To a stirred solution of the 3-aryleulvinic acid dimethylamide (N,N-dimethyl-3-aryl-4-oxopentanamid; 1.0 mol) in t-butanol (60 ml) is added a 40% solution (10% mol) of tetramethylammonium hydroxide in methanol, followed by the dropwise addition of acrylonitrile (53.1 g., 1.0 mol) at room temperature. The mixture is heated at 50 °C for 2 h and is then diluted with chloroform (250 ml). The solution is washed with dilute hydrochloric acid (50 ml), dried with sodium sulfate, and evaporated in vacuo. The residual product is recrystallized from isopropanol.

Amide 1a; yield: 73%; m.p. 125-126 °C.

C₆H₅-N₂O₂ calc. C 70.60 H 7.40 N 10.29 (272.3) found 70.59 7.39 10.31

1.R. (KBr); ν = 2242; 1710; 1640 cm⁻¹.

^H-N.M.R. (CDCl₃); δ = 2.0 (s, 3H, CO-CH₃); 7.25 (m, 4H, CH₂); 2.97, 3.08 (s, 6H, N-CH₂); 3.24 ppm (s, 2H, CH₂-N). Amide 1b; yield: 90%; m.p. 154-155 °C.

C₆H₅-N₂O₂ calc. C 64.54 H 6.32 N 8.86 (316.4) found 63.88 6.29 8.83

Amide 1c; yield: 79%; m.p. 124-125 °C.

C₆H₅-N₂O₂ calc. C 65.04 H 7.28 N 8.43 (332.4) found 65.35 7.29 8.40

3-Acetyl-3-arylehexitoloeic Acids (2a, b, c); General Procedure:

A suspension of the N,N-dimethyl-3-acetyl-3-aryl-6-nitrilohexanamide (1a, b, c; 0.55 mol) in 12% aqueous sodium hydroxide (500 ml) is refluxed for 12 h, then acidified with hydrochloric acid, and extracted with chloroform (3 × 100 ml). The extract is evaporated and the residual product is recrystallized from isopropanol or ethyl acetate.

Diacid 2a; yield: 79%; m.p. 127-129 °C.

C₆H₅-N₂O₂ calc. C 63.63 H 6.10 (264.3) found 63.95 6.25

1.R. (KBr); ν = 1705; 1690 cm⁻¹.

Diacid 2b; yield: 63%; m.p. 170-171 °C.

C₆H₅-N₂O₂ calc. C 58.44 H 5.23 (308.3) found 58.47 5.68

Diacid 2c; yield: 82%; m.p. 189-190 °C.

C₆H₅-N₂O₂ calc. C 59.26 H 6.21 (324.3) found 59.20 6.35

^H-N.M.R. (DMSO-d₆); δ = 1.90 (s, 3H, CO-CH₃); 3.09 ppm (ABq. 2H, CH₂-N); δ = 2.92, δ = 3.26, J = 16, 13 Hz).

N,N-Dimethyl-3-acetyl-3-phenyl (3a) and N,N-Dimethyl-3-acetyl-3-(3,4-dimethoxyphenyl)-hexanamide Acid 3-Amine (3c):

The N,N-dimethyl-3-acetyl-3-aryl-6-nitrilohexanamide (1a, c; 0.29 mol) is added to 65% sulfuric acid (200 ml). The stirred mixture is heated at 80 °C for 1 h, and then poured into water (500 ml). The monoamide which crystallizes from the mixture is isolated by suction and recrystallized from isopropanol.

Monoamide 3a; yield: 73%; m.p. 212-213 °C.

C₆H₅-N₂O₂ calc. C 66.04 H 7.07 N 4.81 (291.3) found 65.91 7.33 4.75

1.R. (KBr); ν = 1720; 1612 cm⁻¹.

^H-N.M.R. (DMSO-d₆); δ = 1.92 (s, 3H, CO-CH₃); 2.85, 3.10 (s, 6H, N-CH₂); 3.25 ppm (s, 4H, N-CH₂).