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III. Some Special Features of the Reactivity of 3-Carboxyacylindoles*

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A number of amides of indole ketoacids are synthesized. 3-Carboxyacylindoles can be converted to the corresponding enol-lactones by treatment with acetic anhydride or acetyl chloride. Reaction of the lactones with ammonia or amines involves lactone ring opening, and this makes it possible to prepare some N-substituted or unsubstituted ketoacid amides. Deacylation can occur in the action of strong bases or high temperatures on indoleketocids. Reaction of 2-((indolyl-3') benzonic acid with dimethyl sulfate proceeds in two ways: the NH group is methylated, and there is conversion to the corresponding indolenine, with subsequent methylation of the enol.

In preceding papers [1-3], we offered a method of synthesizing γ- and δ-ketoacids of the indole series, as well as their functional derivatives of the keto group. It was shown that a carboxyl group in the γ-position makes for certain difficulties in effecting substitution and reduction. To a considerable extent the structures and reactivities of the 3-carboxyacylindoles are conditioned by two factors: firstly, special features of the conjugation of the carbonyl group with the indole ring π-electrons and secondly, the possible occurrence of the γ- and δ-ketoacids in the cyclic hydroxylactone forms. Investigation of the IR spectra of these acids in the solid state [2] made it possible to decide unequivocally in favor of an open structure. But a number of chemical reactions indicate possible formation in solution of cyclic compounds by, for example, intramolecular cyclization of acyl-cations, arising from an open form [4, 5].

Thus under the action of acetyl chloride, γ-((indolyl-3)γ-ketobutyric acid and δ-((indolyl-3)-δ-ketovaleric acid, rather readily enolize to give 40% yields of the enols, acetylation occurring at the nitrogen.

If, however, acetic anhydride in the presence of sodium acetate is used, the yield of enol-lactone I is only 18%.

It can be assumed that partial formation of lactol form also occurs under the action of such acid reagents as hydrochloric acid or phosphorus pentachloride. Apparently, it was for that reason that we could not obtain γ-((indolyl-3)γ-ketobutyryl chloride and effect Clemmensen reduction of it [3].

In alkali the ketoacids studied exist only in the open form. Thus an attempt to convert the above-described enol-lactones to enol lactams by treatment with ammonia leads to lactone ring opening and formation of the corresponding amides of the ketoacids, the structures of these being confirmed by retro-synthesis. Both unsubstituted amides and dimethylamides II of ketobutyric and ketovaleric acids of the indole series were obtained, the best yields (50-70%) being secured by use of the method of mixed anhydrides.

Such ketoamides are of independent interest as intermediates in the synthesis of dihomotryptamines. Actually, lithium aluminum hydride reduction of N, N-dimethyl γ-((indolyl-3)γ-ketobutyramide (II, R = H) leads to formation of 3-((4-dimethylaminobutyl)indole, but the exceptionally low solubility of the starting compound in ether offers considerable experimental difficulty (after 15 hr it was possible to isolate only traces of compound which the IR spectrum showed not to contain carbonyl groups). There is practically no reduction of γ-((indolyl-3)-γ-ketobutyric acid itself under the same conditions. The compound isolated in traces was the corresponding alcohol (lack of absorption bands in the region of carbonyl group vibrations).

The action of lithium aluminum hydride on 2-((indolyl-3') benzonic acid leads not only to reduction of the keto

*For Part II see [1].
group to methylene, but also of the carboxyl group to an alcohol one.

\[
\text{COCH}_2\text{CH}_2\text{COOH} \rightarrow \quad \text{COCH}_2\text{CH}_2\text{CON}^\text{CH}_3
\]

Amides of Indole Ketoacids

<table>
<thead>
<tr>
<th>Name</th>
<th>Mp, °C</th>
<th>Formula</th>
<th>Found, %</th>
<th>Calculated, %</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5)-(Indolyl-3)-(\gamma)-ketovaleramide</td>
<td>150–151</td>
<td>(\text{C}_8\text{H}_14\text{N}_2\text{O}_2)</td>
<td>67,46</td>
<td>6,12</td>
<td>55</td>
</tr>
<tr>
<td>(\gamma)-(2-Methylindolyl-3)-(\gamma)-ketobutyramide</td>
<td>198</td>
<td>(\text{C}_8\text{H}_14\text{N}_2\text{O}_2)</td>
<td>67,55</td>
<td>6,10</td>
<td>54</td>
</tr>
<tr>
<td>(\gamma)-(2-Phenylindolyl-3)-(\gamma)-ketobutyramide</td>
<td>222</td>
<td>(\text{C}_8\text{H}_16\text{N}_2\text{O}_2)</td>
<td>--</td>
<td>9,54</td>
<td>70</td>
</tr>
<tr>
<td>(N, N)-Dimethyl (\gamma)-(Indolyl-3)-(\gamma)-ketobutyramide</td>
<td>180–181</td>
<td>(\text{C}_8\text{H}_16\text{N}_2\text{O}_4)</td>
<td>68,42</td>
<td>6,71</td>
<td>46</td>
</tr>
<tr>
<td>(N, N)-Dimethyl (5)-(Indolyl-3)-(\delta)-ketovaleramide</td>
<td>187–188</td>
<td>(\text{C}_8\text{H}_14\text{N}_2\text{O}_2)</td>
<td>69,78</td>
<td>7,01</td>
<td>65</td>
</tr>
<tr>
<td>(N, N)-Dimethyl (\gamma)-(2-phenyl-indolyl-3)-(\gamma)-ketobutyramide</td>
<td>190–191</td>
<td>(\text{C}_9\text{H}_20\text{N}_2\text{O}_4)</td>
<td>74,64</td>
<td>6,10</td>
<td>57</td>
</tr>
</tbody>
</table>

The action of diazomethane on the keto acids which we have previously described \[2\] gave almost quantitative yields of the corresponding methyl esters. It is proved that methylation of the nitrogen of the indole ring does not occur. We obtained 1-methyl keto acids by use of dimethyl sulfate in alkali. In some cases simultaneous esterification of the carboxyl group was observed. Alkali facilitates formation of an indolenine structure. When \(2-(\text{Indolyl-3'})\) benzoic acid is methylated, compound IV is isolated as a side reaction product (frequencies \(1640 \text{ cm}^{-1} \text{(C=N)}\) and \(1722 \text{ cm}^{-1} \text{(COOCH}_3)\)).

Acid hydrolysis of IV leads not only to formation of the keto form, but to simultaneous alkylation of the nitrogen atom, i.e., to structure V (shown chromatographically, and also by comparison of melting points).

Peculiarities of the keto group at the \(\delta\)-position in the indole ring are further exhibited in the comparative ease of deacylation. It is known that when 3-acylindoles are heated at 200–220° in the presence of alkoxides of alkali metals, the corresponding indole homologs are formed [8]. Actually we isolated 3-ethylindole when \(\gamma\)-(Indolyl-3)-\(\gamma\)-keto-