Reactions with 2-Carboxyindole-3-acetic Acid Imides,
Preparation of Some Imides, their Condensations with Aromatic Aldehydes and Nitroso Compounds and their Coupling with Diazonium Salts

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Pyranocinolones, Pyridocinolones, Coupling, Benzylaition

Heating 2-carboxyindole-3-acetic acid anhydride (1) with primary amines, the cyclic imides 1,2,3,4-tetrahydro-9 H-2-arylpriodo[3,4-b]indole-1,3-diones (2) were obtained. Compounds 2 coupled with diazonium salts to give 4-arylaizo derivatives (3), condensated with aromatic aldehydes afforded 4-arylmethylene derivatives (4). Benzylaition of 2 yielded the 4,4-dibenzy1 derivative (6). 2 reacted also with p-nitrosodimethylaniline to yield the azomethine derivatives (7) which were hydrolysed by hydrocholric/acetic acid mixture to give the triketo compounds (8). The structure assigned to the condensation products have been supported by NMR and IR data.

Examination of the literature revealed that the attempts made to prepare cyclic imides of 2-carboxyindole-3-acetic acid were not successful1.

This work describes the preparation of some imides of 2-carboxyindole-3-acetic acid and investigation of the reactions of these imides. Heating 2-carboxyindole-3-acetic acid anhydrides (1) with primary amines and phosphorus pentoxide in dry xylene resulted in the formation of the cyclic imides of 2-carboxyindole-3-acetic acid (1,2,3,4-tetrahydro-9 H-2-arylpriodo[3,4-b]indole-1,3-diones) (2).

Compound 2e was obtained by the action of heat on the ammonium salt of 2-carboxy-1-methylindole-3-acetic acid in contrast to the work of KERMACK et al.1

\[ \text{IR spectrum of 2e shows two CO bands at 1695 and 1665 cm}^{-1}. \text{The absence of absorption in the OH region is in favour of the diketo structure (2).} \]

The NMR spectrum of 2e shows peaks at 3.88 ppm (s, 5, N-CH\textsubscript{3}), 5.18 ppm (s, 2, CH\textsubscript{2}) and 7.25 ppm (m, 9, aromatic protons).

The cyclic imides (2) coupled with aronediazonium salts in pyridine to yield the corresponding 4-arylaizo derivatives (1,2,3,4-tetrahydro-9 H-2-arylpriodo[3,4-b]indole-1,3,4-trione-4-aryhydrazones) (3).

The IR spectrum of 3d shows two CO bands at 1665 and 1625 cm\textsuperscript{-1}.

The UV spectrum of 3e shows a strong maximum at 456 nm (\(\varepsilon = 37 \times 10^3\)) and a weak maximum at
323 nm \((e = 10 \times 10^3)\), which is in agreement with the hydrazone structure\(^3\)–\(^5\).

Compounds 2d, e condensed with aromatic aldehydes, in presence of piperidene, to give 4-arylmethylene derivatives (4-arylmethylene-1,2,3,4-tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3-diones) (4).

\[
\begin{align*}
4a: R &= H; R' = \text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5 \\
4b: R &= H; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5 \\
4c: R &= \text{CH}_3; R' = \text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5 \\
4d: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5 \\
4e: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5 \\
4f: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5\text{CH} = \text{CH} \\
4g: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5\text{OCH}_3-p \\
4h: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5\text{CH} = \text{CH} \\
4i: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5\text{Cl}-o \\
4j: R &= \text{CH}_3; R' = \text{CH}_2\text{C}_6\text{H}_5; \text{Ar} = \text{C}_6\text{H}_5\text{Cl}-o
\end{align*}
\]

The benzylidene derivative (4d) was reduced by zinc dust and acetic acid to form the 4-benzyl derivative (5) which reacted with benzyl chloride in sodium ethoxide to yield the 4,4-dibenzyl derivative (6). The latter compound was also obtained by the reaction of 2e with excess of benzyl chloride.

\[
\begin{align*}
4d &\xrightarrow{\text{Zn/ACOH}} 5 \\
2e &\xrightarrow{\text{ZPhCH}_2\text{Cl/ EtONa}} 5
\end{align*}
\]

Compounds 2d, e condensed also with \(p\)-nitrosodimethylaniline to yield the azomethine derivatives (7) which were hydrolysed by hydrochloric/ acetic acid mixture to give the triketo compounds (8).

\[
\begin{align*}
7a: R &= \text{C}_6\text{H}_5 \\
7b: R &= \text{CH}_3\text{C}_6\text{H}_5 \\
7c: R &= \text{CH}_3 \\
7d: R &= \text{CH}_3\text{C}_6\text{H}_5 \\
8a: R &= \text{C}_6\text{H}_5 \\
8b: R &= \text{CH}_3\text{C}_6\text{H}_5
\end{align*}
\]

Compound 8b was converted into the corresponding 4-phenylhydrazone derivative (3d) by treatment with phenylhydrazine in acetic acid.

\[
\begin{align*}
8b &\xrightarrow{\text{PhNHNH}_2} 3d
\end{align*}
\]

The triketo derivative (8a) condensed with \(o\)-phenylenediamine to form 6,8-dihydro-8-methyl-6-phenyl-7 H-indolo-3’,2’:4,5- pyrido[2,3-b]quinoxalin-7-one (9).

\[
\begin{align*}
9 &\xrightarrow{\text{EtOC}_2\text{H}_5} 10 \\
10 &\xrightarrow{\text{PhNHNH}_2} 11
\end{align*}
\]

The IR spectrum of 9 shows one band at 1668 cm\(^{-1}\) in the CO region.

Reaction of 2e with ethyl orthoformate, in refluxing acetic anhydride, afforded the 4-ethoxy-arylmethylene derivative (10), which reacted with phenylhydrazine to give 11.

\[
\begin{align*}
11 &\xrightarrow{\text{PhNHNH}_2} 11
\end{align*}
\]

Experimental

Melting points are not corrected. IR spectra were determined as KBr pellets with a Perkin-Elmer 457 grating IR spectrophotometer. NMR spectra were recorded on a Perkin-Elmer R 12 A instrument, with TMS as internal reference. UV spectra were obtained in dioxan solution with a Perkin-Elmer spectrophotometer 402.

1,2,3,4-Tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3-diones (2)

A solution of 0.01 mole of 1 and 0.011 mole of the appropriate amine in 100 ml of anhydrous
xylene, was treated with 5 g of phosphorus pentoxide and the mixtures was refluxed for 2 hours. The pale yellow solution was filtered while hot and the filtrate was evaporated to dryness and the residue was triturated with ethanol to give a pale yellow solid which was crystallised from acetic acid (see Table I).

1,2,3,4-Tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3,4-trione-4-arylhydrazones (3)

A solution of 0.002 mole of 2 in 20 ml of pyridine was cooled in an ice-bath and treated with a solution of an equimolecular amount of the appropriate aryldiazonium salt (prepared from 0.002 mole of the amine in 4 ml of dilute hydrochloric acid (1:1) and 0.2 g of sodium nitrite), left to stand in ice for 1 hour, and diluted with water (ca. 100 ml). The product that separated was filtered off, washed thoroughly with water and crystallised from dioxan (see Table II).

4-Arylmethylene-1,2,3,4-tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3-diones (4)

0.002 mole of 2 was treated with an equimolecular amount of the appropriate aldehyde in presence of one drop of piperidine, and the mixture was warmed for 5 minutes. It was then cooled, triturated with ethanol and the product was collected, washed with ethanol and crystallised from acetic acid (see Table III).

1,2,3,4-Tetrahydro-9 H-2,4-dibenzyl-9-methylpyrido[3,4-b]indole-1,3-dione (5)

The benzylidene derivative (4d) (0.5 g) was dissolved in 50 ml of boiling acetic acid and the hot solution was treated with zinc dust (1 g) in portions. The mixture was boiled for 5 minutes and filtered while hot and the filtrate was diluted with water (25 ml). The product 5, that separated was filtered off, washed with water and recrystallised from ethanol as colourless needles (0.4 g; 66%), m.p. 168-169 °C.

Analysis for C26H22N2O2
Calcd C 79.16 H 5.62 N 7.10, Found C 79.1 H 5.8 N 7.3.

1,2,3,4-Tetrahydro-9 H-2,4,4-tribenzyl-9-methylpyrido[3,4-b]indole-1,3-dione (6)

a) From 5 and benzyl chloride

Half a gram of 5 dissolved in 20 ml of absolute ethanol containing 0.05 g of sodium metal, was

| Table I. 1,2,3,4-Tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3-diones. |
|------------------------|-----------------------------------|-----------------|------------------|-----------------|-----------------|
| Compound | m.p. [°C] | Yield [%] | Formula | Carbon calcd | Carbon found | Hydrogen calcd | Hydrogen found | Nitrogen calcd | Nitrogen found |
| 2a | 282-3 | 53 | C17H12N2O2 | 73.89 | 73.7 | 4.38 | 4.2 | 10.14 | 10.0 |
| 2b | 243 | 60 | C18H14N2O2 | 74.46 | 74.3 | 4.86 | 4.7 | 9.65 | 9.5 |
| 2c | 272 | 60 | C19H14N2O2 | 67.28 | 67.1 | 4.71 | 4.9 | 13.08 | 13.2 |
| 2d | 205 | 50 | C18H14N2O2 | 74.45 | 74.1 | 4.86 | 4.9 | 9.65 | 9.5 |
| 2e | 198-9 | 66 | C19H14N2O2 | 74.98 | 75.2 | 5.30 | 5.5 | 9.21 | 9.2 |
| 2f | 228 | 74 | C19H14N2O2 | 74.98 | 75.1 | 5.30 | 5.1 | 9.21 | 9.2 |
| 2g | 192 | 72 | C20H13N2O2 | 75.45 | 75.2 | 5.70 | 5.9 | 8.80 | 8.8 |

| Table II. 1,2,3,4-Tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3,4-trione-4-arylamides. |
|------------------------|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Compound | m.p. [°C] | Yield [%] | Formula | Carbon calcd | Carbon found | Hydrogen calcd | Hydrogen found | Nitrogen calcd | Nitrogen found |
| 3a | 315 | 80 | C23H16N4O2 | 72.62 | 72.5 | 4.54 | 4.1 | 14.73 | 14.5 |
| 3b | 230 | 90 | C25H20N4O2 | 70.74 | 70.6 | 4.75 | 4.5 | 13.20 | 13.0 |
| 3c | 278 | 85 | C24H18N4O2 | 73.98 | 73.1 | 4.60 | 4.4 | 14.21 | 14.1 |
| 3d | 241 | 95 | C25H20N4O2 | 73.51 | 73.6 | 4.94 | 4.9 | 13.72 | 14.0 |
| 3e | 250 | 92 | C26H22N4O2 | 73.91 | 73.9 | 5.25 | 5.5 | 13.26 | 13.0 |
| 3f | 215 | 72 | C26H22N4O2 | 73.91 | 73.6 | 5.25 | 5.6 | 13.26 | 13.1 |
| 3g | 248 | 80 | C26H22N4O2 | 71.22 | 70.9 | 5.06 | 5.4 | 12.78 | 12.5 |
| 3h | 190 | 73 | C25H19N4O2 | 66.22 | 66.6 | 4.22 | 4.1 | 15.45 | 15.4 |
| 3i | 213 | 70 | C25H19ClN4O2 | 67.79 | 67.6 | 4.32 | 4.5 | 12.65 | 12.6 |

* Cl: Calcd 8.00, Found 8.1%.
Table III. 4-Arylmethylene-1,2,3,4-tetrahydro-9 H-2-arylpyrido[3,4-b]indole-1,3-diones.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Formula</th>
<th>Carbon calcd</th>
<th>Carbon found</th>
<th>Hydrogen calcd</th>
<th>Hydrogen found</th>
<th>Nitrogen calcd</th>
<th>Nitrogen found</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>268</td>
<td>90</td>
<td>C_{24}H_{16}N_{2}O_{2}</td>
<td>79.09</td>
<td>79.1</td>
<td>4.43</td>
<td>4.2</td>
<td>7.69</td>
<td>7.5</td>
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<tr>
<td>4b</td>
<td>273</td>
<td>95</td>
<td>C_{25}H_{18}N_{2}O_{2}</td>
<td>79.34</td>
<td>79.2</td>
<td>4.80</td>
<td>4.5</td>
<td>7.40</td>
<td>7.2</td>
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<tr>
<td>4c</td>
<td>258</td>
<td>95</td>
<td>C_{25}H_{18}N_{2}O_{2}</td>
<td>79.34</td>
<td>79.3</td>
<td>4.80</td>
<td>4.6</td>
<td>7.40</td>
<td>7.1</td>
</tr>
<tr>
<td>4d</td>
<td>198</td>
<td>95</td>
<td>C_{26}H_{20}N_{2}O_{2}</td>
<td>79.57</td>
<td>79.8</td>
<td>5.14</td>
<td>5.3</td>
<td>7.14</td>
<td>7.5</td>
</tr>
<tr>
<td>3e</td>
<td>170</td>
<td>88</td>
<td>C_{27}H_{22}N_{2}O_{3}</td>
<td>76.76</td>
<td>77.1</td>
<td>5.25</td>
<td>5.5</td>
<td>6.63</td>
<td>6.7</td>
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<tr>
<td>3f</td>
<td>254</td>
<td>80</td>
<td>C_{28}H_{22}N_{2}O_{2}</td>
<td>80.36</td>
<td>80.6</td>
<td>5.30</td>
<td>5.4</td>
<td>6.69</td>
<td>6.5</td>
</tr>
<tr>
<td>3g</td>
<td>198</td>
<td>88</td>
<td>C_{26}H_{20}N_{2}O_{3}</td>
<td>76.45</td>
<td>76.2</td>
<td>4.94</td>
<td>5.2</td>
<td>6.86</td>
<td>6.6</td>
</tr>
<tr>
<td>3h</td>
<td>192-3</td>
<td>86</td>
<td>C_{26}H_{19}ClN_{2}O_{2}</td>
<td>73.15</td>
<td>73.4</td>
<td>4.49</td>
<td>4.8</td>
<td>6.56</td>
<td>6.2</td>
</tr>
</tbody>
</table>

* Cl: Calcd 8.30, Found 8.0%.

Treated with 0.2 g of freshly distilled benzyl chloride. The whole was refluxed for 2 hours, diluted with water (10 ml) and cooled. The solid, that separated was filtered off and crystallised from ethanol as colourless crystals of 6, m.p. 170 °C; yield 0.5 g (83%).

Analysis for C_{29}H_{28}N_{2}O_{2}
Calcd C 81.79 H 5.82 N 5.78,
Found C 81.7 H 6.0 N 5.6.

b) From 2e and benzyl chloride

A solution of 1 g of 2e in 50 ml absolute ethanol containing 0.1 g of sodium, was treated with 0.8 g (2 moles) of distilled benzyl chloride. The mixture was refluxed for 2 hours, diluted with water (20 ml) and the solid that separated was collected and crystallised from ethanol as colourless crystals (1 g; 67%), m.p. 170 °C; not depressed when mixed with the compound prepared above.

4-(p-Dimethylaminophenylimino)-1,2,3,4-tetrahydro-9 H-2-aryl-9-methylpyrido[3,4-b]indole-1,3,4-triones (8)

A suspension of 0.005 mole of 2d,e in 50 ml of ethanol was treated with 0.005 mole of p-nitroso-dimethylaniline and one drop of piperidine. The mixture was refluxed for 30 minutes and cooled. The product that separated was filtered off, washed with ethanol and crystallised from benzene to yield 7a,b.

7a formed blue crystals from benzene, m.p. 212 °C; yield 65%.

Analysis for C_{28}H_{22}N_{4}O_{2}
Calcd C 73.91 H 5.25 N 13.26,
Found C 73.7 H 5.1 N 13.0.

7b gave blue crystals from benzene, m.p. 190 °C; yield 62%.

Analysis for C_{27}H_{24}N_{4}O_{2}
Calcd C 74.29 H 5.54 N 12.84,
Found C 73.9 H 5.5 N 12.6.

Condensation of the trione (8b) with phenylhydrazine

A solution of 0.3 g of 8b in 25 ml of glacial acetic acid was treated with 0.1 ml of phenylhydrazine, and boiled for 5 minutes, and cooled. The orange crystals that separated were collected (0.25 g) and recrystallised from acetic acid, m.p. 241 °C; not depressed when mixed with 3d.

6,8-Dihydro-8-methyl-6-phenyl-7 H-indole 3',2':4,5 pyrido[2,3-b]quinazolin-7-one (9)

A mixture of 8a (3 g, 1 mole) and o-phenylenediamine (1.1 g, 1.1 mole) was powdered, then heated in an oil-bath at 140–160 °C for 30 minutes. The resulting solid was washed well with benzine (40–60 °C) and the product 9 was crystallised from dioxan as yellow crystals, m.p. 300 °C; yield 60%.

Analysis for C_{32}H_{32}N_{2}O
Calcd C 72.03 H 4.38 N 14.89,
Found C 71.9 H 4.1 N 14.6.
I.2.3.4-Tetrahydro-9H-2-benzyl-4-ethoxymethylene-9-methylpyrido[3,4-b]indole-1,3-dione (10)

Half a gram of 2e dissolved in 10 ml of acetic anhydride, was treated with 3 ml of ethyl orthoformate and refluxed for 3 hours. On cooling, the crystalline precipitate was filtered off and recrystallised from ethanol as yellow needles, m.p. 185 °C; yield 0.5 g (80%). It gives pink colour with concentrated sulphuric acid.

Analysis for C_{22}H_{20}N_{2}O_{3}
Calcd  C  73.31  H  5.59  N  7.77,
Found  C  73.2   H  5.3   N  7.3.


1,2.3.4-Tetrahydro-9H-2-benzyl-9-methyl-4-phenylhydrazinomethylene-pyrido[3,4-b]indole-1,3-dione (11)

A solution of 0.5 g of 10 in 10 ml of glacial acetic acid was treated with 0.2 ml of phenylhydrazine, and the mixture was boiled for 5 minutes. It was then cooled, diluted with water and the precipitate was collected and crystallised from ethanol as brownish crystals of 11, m.p. 178 °C; yield 0.5 g (80%).

Analysis for C_{26}H_{22}N_{4}O_{2}
Calcd  C  73.91  H  5.25  N  13.26,
Found  C  73.8  H  4.9  N  13.4.

3 C. H. De Puy and P. R. Wells, J. Amer. Chem. Soc. 82, 2909 [1960].


5 H. C. Yao and P. Resnick, J. Amer. Chem. Soc. 84, 3514 [1962].