Synthesis of Hexahydroindazole, Tetrahydro-[pyrimidoquinazolinone, benzodiisoxazolone] Derivatives and Anils from Diethyl 1,4-Cyclohexanedione-2,5-dicarboxylate

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Indazolones, Isoxazolones, Quinazolinones, Synthesis

Treatment of diethyl 1,4-cyclohexanedione-2,5-dicarboxylate (1) with hydrazine hydrate in glacial acetic acid afforded the diazobicyclooctadienedicarboxylate (2) and the azine (3). On the other hand, condensation of 1 with benzenesulphonylhydrazide in ethanolic solution gave the indazole derivative (4). Interaction of 1 with urea or hydroxylamine afforded the tetrahydropyrimidoquinazolinone (5) and the tetrahydrobenzodioxazolone (6), respectively. Treatment of 1 with aniline gave the mono-anil (7) which, when subjected to Japp-Klingemann reaction with p-anisidine gave the dihydrazonoanil (8) and their condensation with benzidine in acetic acid gave the hydrazonoketoester (9). On the other hand condensation of 7 with hydrazine hydrate in ethanolic solution afforded the azobis (5-anilinoterephthalate) (10) and the hexahydrobenzodipryrazolone (11).

Based on our recent work [1, 2] anticipated the main product in the condensation of 1 with hydrazine in acetic acid [3] would be 2,3a,4,6,7a,8-hexahydro-2,6-bis(acetyl)benzo[1,2-C]; 4,5-C] dipyrazole-3,7-dione [1]; but diethyl 2,3-diazabicyclo[2,2,2]octa-(7),4,5,7,8-tetrahydroxylactone dicarboxylate (2) and diethyl 2,5-dioxo-1,4-cyclohexanedicarboxylate-2,2-azine (3) were the only products obtained. The IR spectrum of 2 showed absorption bands at 1685 (CO ester) and 3000 cm⁻¹ (NH). The IR spectrum of 3 showed absorption bands at 1700 (CO amide) and 3500 cm⁻¹ (NH stretching). Further evidence for the structure 5 was obtained from independent synthesis through interaction of monochloroacetic acid with 4a,5,9a,10 - tetrahydro - 2,7 - dithiopyrimido [4,5-g] quinazoline-2,4,7,9(3 H,8 H)-tetrone.

Interaction of 1 with hydroxylamine hydrochloride in pyridine gave 3a,4,7a,8-tetrahydro-3 H,7 H-benzo[1,2 C; 4,5-C]dioxazolo-3,7-dione (6). The IR spectrum showed stretching frequencies at 1650 cm⁻¹ and 1595 cm⁻¹ characteristic for CO and C=N groups.

It has been found that 1,3-indanedione reacts with one mole of aromatic amines in glacial acetic acid to give the mono-anil [4]. Thus, condensation of 1 with one mole aniline in acetic acid afforded diethyl 4-phenylimino-cyclohexanone-2,5-dicarboxylate (7). The IR spectrum of 7 showed well-defined absorption bands attributable to the carbonyl of the ester (1680 cm⁻¹), endocyclic carbonyl (1640 cm⁻¹) and C=N (1600 cm⁻¹).

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Table I. Physical data of compounds 2-10.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Carbon found</th>
<th>Hydrogen found</th>
<th>Nitrogen found</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₈H₈O₄N₂</td>
<td>(2)</td>
<td>111</td>
<td>57.20</td>
<td>6.2</td>
<td>11.1</td>
</tr>
<tr>
<td>C₈H₈O₄N₂O₈</td>
<td>(3)</td>
<td>153</td>
<td>56.5</td>
<td>6.2</td>
<td>5.6</td>
</tr>
<tr>
<td>C₈H₈O₄N₂O₈S</td>
<td>(4)</td>
<td>108</td>
<td>52.7</td>
<td>4.2</td>
<td>7.7</td>
</tr>
<tr>
<td>C₈H₈N₂O₄</td>
<td>(5)</td>
<td>360</td>
<td>48.5</td>
<td>3.1</td>
<td>22.4</td>
</tr>
<tr>
<td>C₄H₄N₂O₄</td>
<td>(6)</td>
<td>360</td>
<td>49.1</td>
<td>3.2</td>
<td>22.5</td>
</tr>
<tr>
<td>C₈H₈N₂O₅</td>
<td>(7)</td>
<td>119</td>
<td>65.3</td>
<td>6.2</td>
<td>4.2</td>
</tr>
<tr>
<td>C₈H₈N₂O₅O₃</td>
<td>(8)</td>
<td>121</td>
<td>68.6</td>
<td>5.5</td>
<td>15.3</td>
</tr>
<tr>
<td>C₂₈H₃₈O₁₀N₈O₁₀</td>
<td>(9)</td>
<td>175</td>
<td>65.25</td>
<td>6.2</td>
<td>4.15</td>
</tr>
<tr>
<td>C₈H₈O₈N₈O₈</td>
<td>(10)</td>
<td>151</td>
<td>65.98</td>
<td>5.71</td>
<td>8.46</td>
</tr>
</tbody>
</table>

* Found: S, 8.9%; Required: S, 8.8%.

Treatment of 7 with two moles of p-anisyl-diazonium chloride gave 5-(phenylmimo-1,2,4-cyclohexanetrione-1,4-bis-(p-methoxyphenyl)hydrazone (8), which revealed endocyclic carbonyl absorption band at 1690 cm⁻¹, C=O, C=N at 1600 cm⁻¹ and NH stretching at 3350 cm⁻¹.

Treatment of 7 with benzidine in acetic acid afforded 9. The formation of 9 finds support from (a) correct analytical data, (b) the IR spectrum and (c) the work of Yokoyama et al. [5] that on the interaction of 1,4-bis(ethoxycarbonyl)-2,5-diamino-1,4-cyclohexadiene and aqueous acetic acid 1 is formed.

Condensation of 7 with hydrazine hydrate in ethanolic solution gave tetaethyl 2,2-azobis(5-anilinoterephthalate) (10) and 2,3a,4,5,6,7a,8-hexahydrobenzo[1,2-C; 4,5-C]diprazole-3,7-dione (11).

Structures 10 and 11 were confirmed from their correct analytical data and infrared spectra. The hexahydridopyrazoledione (11) was identical with that obtained previously by the interaction of 1 with two males of hydrazine in ethanolic solution [1]. The IR spectrum of 10 showed absorption bands at 1590 (N=N), 1700 (CO ester) and 3370 cm⁻¹ (HN). Further evidence for the structure of 10 was obtained from the work of Kauffmann [6] by the interaction of 1 with aromatic amines.

Experimental

Melting point (uncorrected) were determined on Gallenkamp electric melting point apparatus. Infra-red spectra were recorded on KBr discs using a Unicam SP 2000 Infrared Spectrophotometer.

Diethyl-1,4-cyclohexanedione-2,5-dicarboxylate (1)

Compound 1 was prepared according to the procedure of Moore [7]: yield 80%, m.p. 127-128 °C.

Diethyl-2,3-diazabicyclo[2,2,2]octa-1(7),4-diene-5,7-dicarboxylate 2 (Table I)

A mixture of 1 (0.02 mole) and hydrazine hydrate (0.01 mole) in 50 ml glacial acetic acid was heated under reflux condenser for 3 h, left to stand overnight. The solid product that separated was filtered off and recrystallized from ethanol to give compound 2 as a brown-red solid crystals.

Diethyl-1,5-diozo-1,4-cyclohexanedicarboxylate-2,2-azine (3) (Table I)

It was prepared by the above procedure using two moles of hydrazine, to give compound 3 as a brown solid crystals.

Ethyl-3,3a,4,5,6,7-hexahydro-3,5-diozo-2-phenyl-sulphonyl-2 H-indazole-6-carboxylate 4 (Table I)

A mixture of 1 (0.01 mole) and benzenesulphonyldrazide (0.01 mole) in 30 ml ethanol, was heated under reflux for 4 h. The solid product that separated on cooling was filtered off and recrystallized from ethanol to give compound 4 as a pale-yellow powder.

4a,5,9a,10-Tetrahydroprimidof[4,5-g]quinazoline-2,4,7,9(3 H,8 H)-tetraone (5) (Table I)

Method (A): To (0.01 mole) of 1 in (0.01 mole) of ethanolic sodium ethoxide solution, (0.01 mole) of urea was added. The reaction mixture was refluxed for 6 h, left to stand overnight, poured into ice-cold dilute acetic acid (PH 4). The solid product that separated was filtered off, then washed with boiling ethanol, to give compound 5 as a piege solid powder.
Method (B): A mixture of the thio compound [1] (0.01 mole) and monochloreacetic acid (0.02 mole) in 100 ml of water, was refluxed, for 2 h. The solid product that separated was acidified by dissolving in 20 ml (10% sodium hydroxide), and reprecipitated with dilute hydrochloric acid, filtered off, washed with boiling ethanol to give compound 5.

3a,4,7a,8-Tetrahydro-3 H,7 H-benzo[1,2-C:4,5-C]-diisoxazole-3,7-dione (6) (Table I)

A mixture of 1 (0.01 mole) and hydroxylamine hydrochloride (0.021 mole) in 50 ml pyridine, was refluxed for 6 h, left to cool, filtered. The solid product washed with water several times, and crystallized from acetic acid to give compound 6 as deep-brown powder.

Diethyl-4-phenylimino-1-cyclohexanone-2,5-dicarboxylate (7) (Table I)

In 50 ml hot acetic acid (b.p. 70–90 °C) a mixture of 1 (0.02 mole) and aniline (0.01 mole) was heated for 1 h. The solid product obtained on cooling, was crystallized from ethanol to give compound 7 as a reddish solid crystals.

5-(Phenylimino)-1,2,4-cyclohexanetrione-1,4-bis-[(p-methoxyphenyl)hydrazone] (8) (Table I)

To (0.01 mole) of 7, sodium hydroxide (50 ml) (2.5%) was added, left to stand at zero for 24 h. The reaction mixture was diluted with (50 ml) of water, and p-anisyldiazonium chloride (0.02 mole) was added. After the complete addition of the diazonium salt, the pH of the medium was adjusted at 7–8, and left to stand for 12 h at 5 °C. The solid product that separated was filtered, crystallized from ethanol to give compound 8 as a deep-red solid crystals.

Condensation of 7 with benzidine: formation of 9 (Table I)

A mixture of 7 (0.01 mole) and benzidine (0.01 mole) in acetic acid 30 ml was heated at (70–90 °C) for 1 h, left to cool. The solid product that separated was crystallized from acetic acid to give compound 9 as a deep-red solid crystals.

Tetraethyl-2,2-azobis(5-anilinoterephthalate) (10) (Table I) and 2,3a,4,6,7a,8-hexahydrobenzo[1,2-C:4,5-C]dipyrazole-3,7-dione (11)

Hydrazine hydrate (0.012 mole) and 7 (0.01 mole) in 30 ml ethanol was refluxed for 4 h, left to cool. The solid product that separated was filtered off and crystallized from methanol to give compound 10 as a red solid crystals, while the insoluble material washed several times with boiling ethanol and proved to be 11 (m.p. and mixed m.p.).