Synthesis of Hexahydroindazole, Tetrahydro-[pyrimidoquinazolinone, benzodioxidazolone] 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 in glacial acetic acid afforded the diazo bicyclooctadinedicarboxylate (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 tetrahydropropyrimidoquinazolinone (5) and the tetrahydrobenzodioxide-isoxazolone (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 hexahydrobenzodipyrazolone (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 3a,4,5,6,7,8-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-diene-5,7-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 ester), 3000 cm⁻¹ (NH), 1650 cm⁻¹ (CO ketone) and 1585 cm⁻¹ (C=N).

Treatment of 1 with one mole of benzenesulphonylhydrazide afforded ethyl 3,5a,4,5,6,7-hexahydro-4,5-dioxo-2-phenylsulphonyl-2 H-indazole-6-carboxylate (4). The IR spectrum showed the regular absorption bands of the pyrazole moiety. Reaction of 1 with urea in ethanolic sodium ethoxide solution afforded 4a,5,9a,10-tetrahydro-4-phenyliminocyclohexanone-2,5-dicarboxylate (7). The IR spectrum 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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Anil [4]. Thus, condensation of 1 with one mole aniline in acetic acid afforded diethyl 4-phenyliminocyclohexanone-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>C_{12}H_{16}O_{2}N_{2} (2)</td>
<td>111</td>
<td>90</td>
<td>57.20</td>
<td>6.2</td>
<td>11.1</td>
</tr>
<tr>
<td>C_{21}H_{22}O_{10}N_{2} (3)</td>
<td>153</td>
<td>70</td>
<td>56.5</td>
<td>6.2</td>
<td>6.34</td>
</tr>
<tr>
<td>C_{16}H_{24}N_{4}O_{8}S* (4)</td>
<td>108</td>
<td>65</td>
<td>52.7</td>
<td>4.2</td>
<td>7.68</td>
</tr>
<tr>
<td>C_{15}H_{20}N_{4}O_{4} (5)</td>
<td>360</td>
<td>80</td>
<td>48.5</td>
<td>3.1</td>
<td>14.3</td>
</tr>
<tr>
<td>C_{24}H_{20}N_{4}O_{8} (6)</td>
<td>360</td>
<td>60</td>
<td>49.19</td>
<td>3.2</td>
<td>14.3</td>
</tr>
<tr>
<td>C_{15}H_{17}N_{5}O_{4} (7)</td>
<td>119</td>
<td>75</td>
<td>65.3</td>
<td>6.2</td>
<td>4.22</td>
</tr>
<tr>
<td>C_{26}H_{22}N_{5}O_{3} (8)</td>
<td>121</td>
<td>45</td>
<td>68.6</td>
<td>5.6</td>
<td>15.38</td>
</tr>
<tr>
<td>C_{36}H_{40}N_{2}O_{10} (9)</td>
<td>175</td>
<td>40</td>
<td>65.25</td>
<td>6.2</td>
<td>41.5</td>
</tr>
<tr>
<td>C_{26}H_{52}N_{4}O_{8} (10)</td>
<td>151</td>
<td>30</td>
<td>65.2</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-(phenylmino)-1,2,4-cyclohexanetione-1,4-bis-(\( p \)-methoxyphenyl)hydrazone, which revealed endocyclic carbonyl absorption band at 1690 cm\(^{-1}\), \( \text{C} = \text{O} \), \( \text{C} = \text{N} \) at 1600 cm\(^{-1}\) and \( \text{N-H} \) 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.

![Chemical structures](attachment:structures.png)

Condensation of 7 with hydrazine hydrate in ethanolic solution gave tetraethyl 2,2-azobis(5-anilinoterephthalate) (10) and 2,3a,4,5,6,7-hexahydro-3,5-dioxo-2-phenyl-diazirine-4a,5,9a,10-tetrahydropyrimidof4,5-g/quinazoline-2,4,7,9(3 H,8 H)-tetrone (5). It was prepared by the above procedure using two moles of hydrate, to give compound 3 as a brown solid crystals.

Experimental

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

**Diethyl-1,4-cyclohexanone-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 hydrate, to give compound 3 as a brown solid crystals.

**Ethyl-3a,4,5,6,7-hexahydr-3,5-diozo-2-phenylsulphonyl-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.
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-3H,7H-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 was 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-aminoterephthalate) (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 was washed several times with boiling ethanol and proved to be 11 (m.p. and mixed m.p.).