Reactions with Cyclic Amidenes III: 
Synthesis of Some New Fused Pyrazole Derivatives

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Diazobetaienes, Dipolareycloaddition, Pyrazolo[4,3-c]-1,2,3,4-tetrazines, 
Ethoxycarbonyl Isothiocyanate, H NMR

Diazotised 5-amino-3-hydroxy-4-phenylazopyrazole (1a) and 3,5-diamino-4-phenylazopyrazole (1b) coupled with active methylene reagents to yield the pyrazolo[1,5-c]-as-triazine derivatives (3a, b, 5a, b). On the other hand coupling of diazotised 1a, with \( \beta \)-naphthal has afforded the acyclic azo derivative (6).

Whereas diazotised 1a underwent intramolecular cyclisation into the pyrazolo[1,5-c]-1,2,3,4-tetrazine derivative (8) on attemptet addition to acrylonitrile, diazotised 1b reacted with acrylonitrile under the same conditions to yield the pyrazolo[1,5-c]-pyridazine derivative (4).

Compounds 1a, b reacted with benzoylisothiocyanate to yield the pyrazol-5-ylthiourea derivatives (10a, b). Whereas 10a readily cyclised into the pyrazolo[3,4-c]-as-triazine derivative (11) on refluxing with pyridine, compound 10b hydrolysed under the same conditions into the pyrazol-5-ylthiourea derivative (12).

The considerable biological activities of fused pyrazoles as adenine analogues CAMP phosphodiesterase inhibitors and as active CNS agents [1–5] has stimulated considerable recent research for the synthesis of these derivatives. In the present paper we report our further results in this direction.

Diazotised 5-aminoazopyrazoles has been reported to couple with \( \beta \)-diketones, \( \beta \)-keto esters, malononitrile and with ethyl cyanoacetate to yield hydrazones which spontaneously cyclised into pyrazolo[1,5-c]-as-triazines. On the other hand, pyrazole-5-diazonium salts reacted with dipolarophiles, in basic media, to yield pyrazolo[1,5-c]-as-triazines \( \text{via} \) 4 + 2 dipolar addition [7, 11, 12]. Now, it has been found that 5-amino-3-hydroxy-4-phenylazopyrazole (1a) and 3,5-diamino-4-phenylazopyrazole (1b) [13] reacted with nitrous acid in presence of concentrated hydrochloric acid-acetic acid mixture to yield the corresponding diazonium salts (2a, b). These could not be isolated in pure state, however, their formation could be observed \( \text{via} \) coupling with active methylene reagents to yield the corresponding pyrazolo[1,5-c]-as-triazine derivatives. Thus with ethyl acetoacetate, ethyl cyanoacetate and with malononitrile the [1,5-c]-as-triazine derivatives (3–5a) were obtained in good yields. Coupling of 1a with \( \beta \)-naphthal has afforded the corresponding phenylazo derivative (6). The formation of 6 is in contrast to the reported formation of pyrazolo-[1,5-c]-as-triazine \( \text{via} \) 4 + 2 dipolar addition on treatment of diazotised aminopyrazoles with naphthols [14].

The reactivity of diazotised 1a, b toward dipolarophiles was also investigated. In contrast to the reported reactivity of diazotised 5-diazo pyrazoles 1a did not add to acrylonitrile. The pyrazolo[3,4-c]-1,2,3,4-tetrazine derivative (7) was the only isolated product. The formation of 7 may be assumed to proceed \( \text{via} \) formation of the intermediate resonance stabilised diazobetaine (8) which undergoes intramolecular cycloisation to afford 7. In contrast to the behaviour of diazotised 1a, diazotised 1b reacted with acrylonitrile to yield a product for which structure 9 was suggested based on analytical and spectral data. Although the mechanism of formation of 9 is not yet clear it may be assumed to proceed \( \text{via} \) the mechanism demonstrated in Chart 1. Further investigation on this matter is now performed.

Recently it has been shown that 1a reacts with benzoylisothiocyanate to yield the corresponding
thiourea derivative. The latter could be cyclised under different conditions to yield different polycyclic products. In the present investigation it has been found that 1b, c react similarly with benzoyl isothiocyanate to yield the corresponding pyrazol-5-ylthiourea derivatives (10a, b). This is in contrast to the reported formation of 1-thiocarbamoyl-3,5-diamino-4-arylaapryrazoles on treatment of 1a with methyl and/or benzyl isothiocyanates [15]. Compound 1c also reacted with ethoxycarbonyl isothiocyanate to yield the corresponding thiourea derivative (9e). The structure assigned for 10a–c was based on analytical, IR, and NMR data. Compound 10a readily cyclised into the pyrazolo[3,4-c]-astrapiazine derivative (11) on refluxing in pyridine. On the other hand, attempted cyclisation of 10b
Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) with a Pye Unicam IR 20. 1H NMR were obtained with a 100 Hz and chemical shifts are expressed as δ ppm.

Reaction of diazotised 1a, b with active hydrogen compounds

General procedure: A solution of each of 1a, b (0.01 mol) in acetic acid (30 ml) and hydrochloric acid (3 ml; 37.5%) was treated with a solution of 0.01 mol of sodium nitrite dissolved in the least amount of water. The resulting solution was then added to a solution of the appropriate active hydrogen compound. The solid product, formed on standing, was collected by filtration and crystallised from the proper solvent (cf. Table I). The IR data of compounds 3a-6 are listed in Table II.

3-Hydroxy-5-phenylpyrazolo[3,4-c]-1,2,3,4-tetrazine (7)

A solution of diazotised 1a (prepared as has been previously described) was kept overnight at room temperature then evaporated in vacuo. The remain-

Table I. List of products of diazotised 1a, b with active hydrogen compounds (3a-6).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>m.p.  [°C]</th>
<th>Yield [%]</th>
<th>Mol. formula</th>
<th>Found (Calcd)</th>
<th>Analysis [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>DMF-water</td>
<td>280</td>
<td>75</td>
<td>C13H14N6O2</td>
<td></td>
<td>55.2 4.3 25.5</td>
</tr>
<tr>
<td>3b</td>
<td>DMF-water</td>
<td>225</td>
<td>70</td>
<td>C15H15O2N7</td>
<td></td>
<td>55.3 4.4 30.3</td>
</tr>
<tr>
<td>4a</td>
<td>DMF-water</td>
<td>275</td>
<td>80</td>
<td>C14H13O2N7</td>
<td></td>
<td>51.1 4.3 30.0</td>
</tr>
<tr>
<td>4b</td>
<td>Ethanol</td>
<td>280</td>
<td>70</td>
<td>C14H14O2N8</td>
<td></td>
<td>51.0 4.2 34.0</td>
</tr>
<tr>
<td>5a</td>
<td>DMF-water</td>
<td>280</td>
<td>70</td>
<td>C12H8ON8</td>
<td></td>
<td>51.4 3.0 40.0</td>
</tr>
<tr>
<td>5b</td>
<td>DMF-water</td>
<td>280</td>
<td>65</td>
<td>C12H9N9</td>
<td></td>
<td>51.8 3.8 45.2</td>
</tr>
<tr>
<td>6</td>
<td>DMF-water</td>
<td>235</td>
<td>70</td>
<td>C19H14O2N6</td>
<td></td>
<td>64.0 4.0 23.5</td>
</tr>
</tbody>
</table>

Table II. IR spectral data of compounds 3a, b-6a (cm⁻¹); selected bands.

<table>
<thead>
<tr>
<th>Compound</th>
<th>δNH₂</th>
<th>CO</th>
<th>CN</th>
<th>NH and/or OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>—</td>
<td>1670</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3b</td>
<td>1635</td>
<td>1725</td>
<td>—</td>
<td>3240, 3300, 3440</td>
</tr>
<tr>
<td>4a</td>
<td>1640</td>
<td>1710</td>
<td>—</td>
<td>br., 3150-3390, 3410</td>
</tr>
<tr>
<td>5a</td>
<td>1640</td>
<td>1670</td>
<td>2240</td>
<td>3390</td>
</tr>
<tr>
<td>5b</td>
<td>1650</td>
<td>—</td>
<td>2240</td>
<td>br., 3100-3400</td>
</tr>
<tr>
<td>6</td>
<td>1660</td>
<td>—</td>
<td></td>
<td>3420 OH</td>
</tr>
</tbody>
</table>
ing solid product was triturated with water, collected by filtration and crystallised from ethanol.

Compound 7 formed brown crystals m.p. 220 °C; yield 80%; IR: 1670 cm⁻¹ (N= N); 2970, 3100 and 3400–3500 cm⁻¹ (chelated NH and OH).

**Analysis for C₅H₆ON₆**

Caled C 50.5 H 2.8 N 39.2,
Found C 49.9 H 2.5 N 39.3.

3-Amino-6,7-dihydro-1-phenyl-7-cyanopyrazole-[3,4-c]-pyridazine (9)

A solution of 0.01 mol of diazotised 1b (prepared as has been previously described), was added to a solution of 0.015 mol of acrylonitrile in 100 ml of ethanol. The reaction mixture was kept overnight at room temperature then evaporated in vacuo. The remaining solid product was then triturated with water and, collected by filtration and crystallised from DMF-water mixture.

Compound 9 formed brown crystals m.p. 280 °C; yield 75%; IR: 1630 (δNH₂), 2250 cm⁻¹ (ester CO), 3220-3300, 3420 (γNH) bands. ¹H NMR: 1.25 (t, 3H, CH₃), 4.3 (q, 2H, CH₂), 7.23-7.9 (m, 12H, 2C₆H₅ and NH₂), 11.4 (1H, lost after D₂O exchange; NH) and 12.1 (1H, lost after D₂O exchange; NH).

**Analysis for C₁₂H₁₅N₆**

Caled C 60.4 H 4.2 N 35.2,
Found C 60.6 H 4.5 N 35.0.

N-(5-Amino-4-phenylazopyrazol-3-yl)-N'-acylthioureas (10a-g)

To a solution of 0.01 mol of benzoyl or ethoxy carbonyl isothiocyanate (prepared as has been previously described) in 100 ml of acetonitrile, 0.01 mol of each of 1b, c were added. The reaction mixture was refluxed for 90 min then evaporated in vacuo. The product was triturated with water and the remaining product was collected by filtration and crystallised from the proper solvent.

Compound 10a, formed yellow crystals from acetone-water mixture; m.p. 122 °C; yield 65%. IR: 1650 cm⁻¹ (ester CO), 3220-3450 cm⁻¹ (γNH groups).

**Analysis for C₁₇H₁₄ON₅S**

Caled C 55.9 H 4.1 N 26.8 S 8.7,
Found C 56.0 H 4.3 N 27.0 S 8.9.

Compound 10b, formed yellow crystals from DMF-ethanol; m.p. 215 °C; yield 70%. IR:

1620 cm⁻¹ (δNH₂), 1710 cm⁻¹ (benzoyl CO), 3300 to 3400 (γNH).

**Analysis for C₁₉H₁₉ON₅S**

Caled C 62.8 H 4.6 N 22.3 S 7.2,
Found C 62.6 H 4.3 N 22.2 S 7.2.

Compound 10e formed yellow crystals from methanol; m.p. 175 °C; yield 70%. IR: 1630 cm⁻¹ (δNH₂), 1725 cm⁻¹ (ester CO), 3220–3300, 3420 (γNH) bands. ¹H NMR: 1.25 (t, 3H, CH₃), 4.3 (q, 2H, CH₂), 7.23-7.9 (m, 12H, 2C₆H₅ and NH₂), 11.4 (1H, lost after D₂O exchange; NH) and 12.1 (1H, lost after D₂O exchange; NH).

**Analysis for C₁₅H₁₉O₂N₇**

Caled C 55.7 H 4.6 N 23.9 S 7.8,
Found C 55.9 H 5.0 N 24.01 S 8.1.

7-Amino-3-benzoylamino-2-phenylpyrazolo[3,4-c]-as-triazine (11)

A solution of 10a (2.0 g) in pyridine (30 ml) was refluxed for 5 h. The solvent was then removed in vacuo and the remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallised from methanol-water mixture.

Compound 11 formed pale yellow crystals; m.p. 212 °C; yield 65%.

**Analysis for C₁₇H₂₀ON₇**

Caled C 61.6 H 3.9 N 29.6,
Found C 61.5 H 3.1 N 30.0.

1-(3-Amino-1-phenyl-4-phenylazopyrazole-5-yl)thiourea (12)

A solution of 10b (2.0 g) in pyridine (30 ml) was refluxed for 5 h. The solvent was then removed in vacuo and the remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallised from methanol-water mixture.

Compound 12 formed yellow crystals; m.p. 165 °C; yield 70%. IR: 1660 cm⁻¹ (δNH₂), 3320 to 3460 cm⁻¹ (γNH).

**Analysis for C₁₉H₁₈O₅N₇**

Caled C 56.9 H 4.4 N 29.0 S 9.5,
Found C 56.6 H 4.7 N 29.0 S 9.0.

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