Synthesis of Some Pyrazolo [Diazepine, Pyrazole, Isoxazole and Pyrimidine] Derivatives and Related Compounds

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5-Pyrazolone Derivatives

4-Arylidene-3-methyl-1-phenyl-2-pyrazolin-5-ones (1a-d) undergoes condensation with diethylmalonate, p-nitroacetophenone and/or 3-acetyl-pyridine under Michael condition to give compounds 2, 3 and 4, respectively. Treatment of 3 and 4 with hydrazine afforded the pyrazolodiazepines 7 and 8, respectively. Interaction of 1a with diethyl phenylmalonate gave the Michael product 9, which undergoes hydrolysis, decarboxylation and cyclisation to give the indanone derivative (11). Condensation of 1c with hydrazine, hydroxylamine and urea gives compounds 12, 13 and 14, respectively. Cyclisation of the Michael compound 15 gives the benzoypyrano-pyrazole (14). When 1e was subjected to Riemer-Tiemann reaction gives compounds 17 and 18. Acetic anhydride treatment of 18 gives the acetyl cresotic acid derivative (19).

3-Methyl-1-phenyl-2-pyrazolin-5-one easily undergoes condensation with aromatic aldehydes to give 1a-d. Compound 1d is condensed with diethyl malonate, p-nitroacetophenone and or 3-acetyl pyridine in presence of sodium methoxide to give the Michael adducts namely diethyl[p-methoxy-a-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]malonate (2), 4-[p-methoxy-a-(p-nitrobenzoylmethyl)benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (3) and 4-[p-methoxy-a-(nicotinoylmethyl)benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (4) respectively. Structure 2 is inferred from the correct analytical data, and its IR spectrum, which shows absorption bands assigned to ester carbonyl (1750 cm\(^{-1}\)), C = N (1615 cm\(^{-1}\)) and C-O stretching (1035 cm\(^{-1}\)). The formation of 3 and 4 finds support from the work of Wiley et al. [1], on the formation of 1,5-pentane-dione derivatives from the Michael addition of aryl methyl ketones.

Reaction of 2 with urea and/or thiourea in presence of sodium methoxide, affords 5-[p-methoxy-a-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]-2-barbituric acid (5) and the corresponding 2-thiobarbituric acid (6) respectively.

The condensation of 1,5-diketones with hydrazines is reported earlier [1] as a route for the synthesis of diazepins. Treatment of 3 and 4 with hydrazine, affords 1,4,5,8-tetrahydro-4-(p-methoxyphenyl)-3-methyl-1-phenyl-6-(p-nitrophenyl)-pyrazolo-[3,4-C][1,2]diazepine (7) and the corresponding 6-(3-pyridyl) derivative (8) respectively.

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In addition to the correct analytical data, the structure of compounds 7 and 8 is confirmed by the IR spectra, in which carbonyl absorption bands disappear, and the (NH) stretching is observed at 3400 cm\(^{-1}\).

On the other hand, reaction of 1a and diethyl phenylmalonate leads the formation of diethyl[a-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]phenylmalonate (9). Compound 9 undergoes hydrolysis and decarboxylation to give \( \alpha,\beta \)-diphenyl-\( \beta \)-(3-methyl-1-phenyl-2-pyrazolin-5-one-4-yl)propionic acid (10). Cyclization of 10 with polyphosphoric acid leads to the formation of 3-methyl-4-(3-oxo-2-phenyl-1-indanyl)-1-phenyl-2-pyrazolin-5-one (11). Structure of 11 is based on elemental analysis and IR spectrum, which shows bands attributable to five ring endocyclic ketone (1735 cm\(^{-1}\), CO (1690 cm\(^{-1}\)) and C=N (1600 cm\(^{-1}\)). The cyclization of \( \beta \)-arylpropionic acid has been reported as a route for the synthesis of indanones [2].

Condensation of 1c with hydrazine in ethanol gives \( p \)-(2,3,3a,6-tetrahydro-4-methylpyrazolo[3,4-C]pyrazol-3-yl)phenol (12), while with hydroxyamine in pyridine lead to the formation of the corresponding pyrazoloisoxazole derivative (13). Condensation of 1d with urea affords 1,3a,4,5-tetrahydro-4-(p-methoxyphenyl)-3-methyl-1-phenyl-6H-pyrazolo[3,4-d]pyrimidin-6-one (14).

The formation of 12–14 is similar to those reported by Zimaitis et al. [3] and Sammour et al. [4–6]. Supporting evidence for the structures of these compounds is provided by elemental analysis and IR spectra.

Treatment of 1b with nitromethane under Michael conditions affords 15 which undergoes cyclization on treatment with acetic hydrochloride acid mixture (1:1) to give 1,4-dihydro-3-methyl-4-(nitromethyl)-1-phenyl[1]benzopyran-2,3-C]pyrazole (16). Besides correct elemental analysis, the structure of 16 is confirmed by the IR spectrum, in which bands corresponding to the absorption of the pyrazolone carbonyl and the phenolic hydroxyl groups are not observed.

Treatment of 1c with chloroform or carbon tetrachloride in presence of potassium hydroxide give \( \alpha \)-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-ylidene)-2,5-cresotaldehyde (17) and the corresponding 2,5-cresotic acid (18) respectively. Acetic anhydride treatment of 18 give the \( o \)-acetyl derivative (19).

In addition to the correct analytical data, the structure of 17, 18 and 19 is confirmed by IR spectra.

Experimental

The melting points reported are uncorrected and determined by the capillary tube method, Infrared spectra is determined on KBr discs using a Unicam SP 1000 Infrared Spectrophotometer.

4-Arylidene-3-methyl-2-pyrazolin-5-ones (1a–d)

These compounds were prepared adopting the procedure of treating 3-methyl-1-phenyl-2-pyrazolin-5-one with the appropriate aromatic aldehydes [7–10].

Condensation of (1d) with diethyl malonate, \( p \)-nitroacetophenone and 3-acetyl pyridine: formation of 2–4 (Table I).

A mixture of the equimolar quantities of (1d) and diethyl malonate or \( p \)-nitroacetophenone or 3-acetyl pyridine is refluxed in absolute methyl alcohol for 6 h in presence of sodium methoxide (3%). The reaction mixture is allowed to stand over night and then acidified by dil. HCl. The solid product so obtained is crystallised from ethylalcohol
Table I. Physical data of compounds 2–19.

<table>
<thead>
<tr>
<th>Compound</th>
<th>m.p. [°C]</th>
<th>Yield [%]</th>
<th>Colour</th>
<th>Mol. formula</th>
<th>Elemental analysis</th>
<th>Hydrogen Found</th>
<th>Caled</th>
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<td></td>
<td></td>
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<td>Carbon Found</td>
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<td>72.62</td>
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<td>62.86</td>
<td>6.5</td>
</tr>
<tr>
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<td>135</td>
<td>75</td>
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<td>60.01</td>
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<tr>
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<td>67.68</td>
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<td>4.3</td>
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</table>

to give the corresponding Michael products 2, 3 and 4 respectively.

Condensation of 2 with urea and thiourea: formation of 5 and 6 (Table I)
A solution of 2 (0.1 mole) in absolute methyl alcohol (50 ml) was treated with urea and/or thiourea (0.12 mole). The reaction mixture was refluxed for 10 h with sodium methoxide (3%), set aside at room temperature for 24 h and then acidified with acetic acid. The product was filtered and crystallised from ethyl alcohol.

Reaction of 3 and 4 with hydrazine: formation of the diazepines 7 and 8 (Table I)
To a solution of 3 and/or 4 (0.1 mole) in ethyl alcohol (50 ml), hydrazine hydrate (0.1 mole) was added and then reaction mixture refluxed for 8 h in the presence of few drops of formic acid. The solid product formed after removal of the solvent was crystallised from ethyl alcohol.

Reaction of 1a with diethyl phenylmalonate: formation of 9 (Table I)
The reaction is similar to those described above for 1d with the active methyl or methylene components.

Hydrolysis and decarboxylation of 9: formation of 10 (Table I)
A solution of 9 (0.1 mole) in potassium hydroxide (20 ml, 3%) is refluxed for 1 h. The reaction mixture is acidified by dil. HCl. The hydrolysed solution is refluxed an additional 1 h, poured into ice-cold water and the solid product so obtained is crystallised from methyl alcohol.

Cyclization of 10: formation of 11 (Table I)
Compound 10 (0.01 mole) is heated with polyphosphoric acid in an oil bath at 140 °C for 1 h. The reaction mixture is poured into ice-cold water, the precipitated compound is collected and crystallised from methyl alcohol.

Condensation of 1c with hydrazine: formation of 12 (Table I)
To a solution of 1c (0.01 mole) in either ethanol or acetic acid (30 ml), hydrazine hydrate (0.01 mole) is added and the reaction mixture refluxed for 6 h. The solid product formed after cooling is crystallised from acetic acid or ethanol.

Condensation of 1c with hydroxylamine hydrochloride formation of 13 (Table I)
A mixture of 1c (0.01 mole), hydroxylamine hydrochloride (0.01 mole) and pyridine (30 ml) is refluxed for 5 h, cooled and acidified with ice-cold dil. acetic acid. The solid product obtained crystallizes from ethanol.

Condensation of 1d with urea: formation of 14 (Table I)
A mixture of 1d (0.01 mole), urea (0.01 mole), dil. HCl (10 ml) and ethanol (20 ml) is refluxed for 8 h. After concentration and cooling, the mixture is boiled with NaOH (50 ml, 5 N). The precipitated product was collected and crystallized from ethanol.

Action of nitromethane on 1b: formation of 15 (Table I)
A solution of 1b (0.1 mole) and nitromethane (0.12 mole) in methanol (60 ml) is heated for 30 min in the presence of few drops of (KOH 50%). The
reaction mixture is left to stand overnight, acidified by dil. HCl and then diluted with water. The solid product obtained is crystallized from ethanol.

Cyclization of 15: formation of 16 (Table I)

To compound 15 (0.1 mole), acetic-hydrochloric acid mixture (10 ml, 1:1) was added with occasional shaking. The mixture was heated on water bath for 2 h, cooled and then diluted with water. The precipitated compound was crystallized from ethyl alcohol.

Reimer-Tiemann reaction on 1c: formation of 17 and 18 (Table I)

To a solution of 1c (0.14 mole) in ethyl alcohol (60 ml) was added NaOH solution (80 ml, 50%) with stirring. Chloroform and/or carbon tetrachloride (0.2 mole) in dropwise was added to the reaction mixture at 70–80 °C. Stirring was continued for 1 h after all chloroform and/or carbon tetrachloride has been added. The solvent was removed under reduced pressure. The residue was acidified by dil. HCl and the solid product so obtained was crystallized from water-ethanol mixture (1:1).

Acetylation of 18: formation of 19 (Table I)

A mixture of 18 (0.1 mole), acetic anhydride (30 ml) and conc. H$_2$SO$_4$ (5 ml) is refluxed on a water bath (50–60 °C) for 15 minutes. The reaction mixture was poured into ice-cold water (150 ml), the solid product so obtained was crystallized from ethanol.