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

El-Sayed Afsah, Fathy A. Amer*, and Momdouh Soafan

Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

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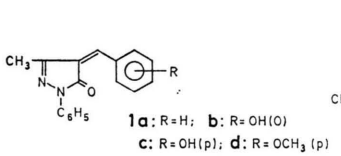
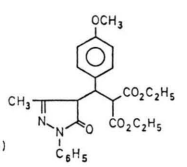
5-Pyrazolone Derivatives

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 benzopyranopyrazole (**14**). When **1c** 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-*α*-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]-malonate (**2**), 4-[*p*-methoxy-*α*-(*p*-nitrobenzoylmethyl)benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (**3**) and 4-[*p*-methoxy-*α*-(nicotinoylmethyl)benzyl]-3-methyl-1-phenyl-2-pyrazolin-5-one (**4**) respectively.





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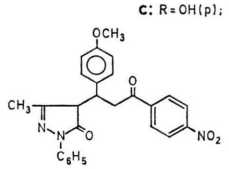

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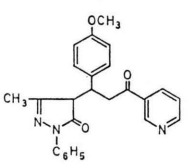

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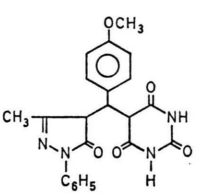
Structure **2** is inferred from the correct analytical data, und its IR spectrum, which shows absorption bands assigned to ester carbonyl (1750 cm^{-1}), C = N (1615 cm^{-1}) and C–O stretching (1035 cm^{-1}). The formation of **3** and **4** finds support from the work of Wiley *et al.* [1], on the formation of 1,5-pentanedione 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-*α*-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]-2-barbituric acid (**5**) and the corresponding 2-thiobarbituric acid (**6**) respectively.



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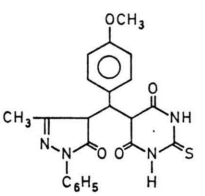

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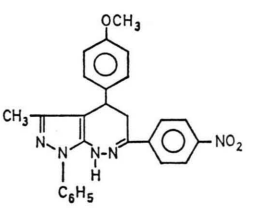
The condensation of 1,5-diketones with hydrazines is reported earlier [1] as a route for the synthesis of diazepins. Treatment of **3** and **4** with hydrazine, affords 1,4,5,8-tetrahydro-4-(*p*-methoxyphenyl)-3-methyl-1-phenyl-6-(*p*-nitrophenyl)-pyrazolo-[3,4-*C*][1,2]diazepine (**7**) and the corresponding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



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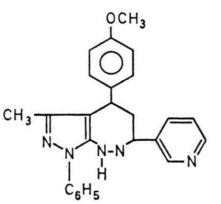

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* Reprint requests to Dr. F. A. Amer.

Present address: Department of Chemistry, Faculty of Science, King Abdulaziz University, P.O. Box 1540 Jeddah, Saudi Arabia.

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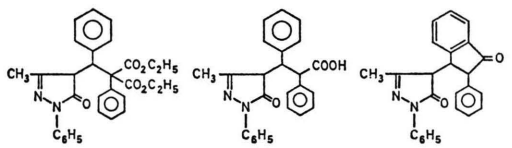
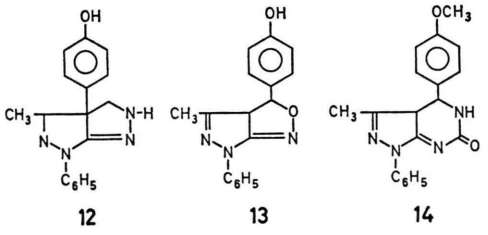
In addition to the correct analytical data, the structure of compounds **7** and **8** is confirmed by the IR spectra, in which carbonyl absorption bands disappear, and the (NH) stretching is observed at 3400 cm^{-1}.

On the other hand, reaction of **1a** and diethyl phenylmalonate leads the formation of diethyl[α-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)benzyl]-phenylmalonate (**9**). Compound **9** undergoes hydrolysis and decarobxylation to give α,β-diphenyl-β-(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 β-arylpropionic acid has been reported as a route for the synthesis of indanones [2].

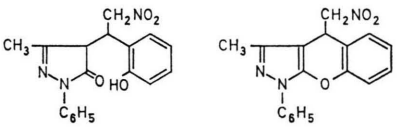


Condensation of **1c** with hydrazine in ethanol gives *p*-(2,3,3a,6-tetrahydro-4-methylpyrazolo[3,4-*C*]pyrazol-3-yl)phenol (**12**), while with hydroxylamine in pyridine lead to the formation of the corresponding pyrazoloisoxazole derivative (**13**). Condensation of **1d** with urea affords 1,3a,4,5-tetrahydro-4-(*p*-methoxyphenyl)-3-methyl-1-phenyl-6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

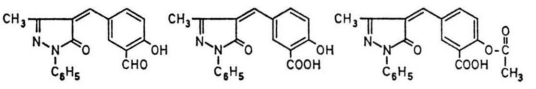


The formation of **12–14** is similar to those reported by Zimaity *et al.* [3] and Sammour *et al.* [4–6]. Supporting evidence for the structures of these compounds is provided by elemental analysis and IR spectra.

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[I]benzopyrano[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 oberved.



Treatment of **1c** with chloroform or carbon tetrachloride in presence of potassium hydroxide give α-(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 capilary 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 addopting 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 pyridene: 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**.

Compound	m.p. [°C]	Yield [%]	Colour	Mol. formula	Elemental analysis Carbon Found	Carbon Calcd	Hydrogen Found	Hydrogen Calcd
2	131	70	yellow	$C_{25}H_{28}N_2O_6$	65.9	66,37	6.16	6.2
3	135	75	orange	$C_{26}H_{23}N_3O_5$	68.27	68.27	4.72	5.03
4	157	75	yellow	$C_{25}H_{23}N_3O_3$	72.36	72.62	5.19	5.61
5	135	75	yellow	$C_{22}H_{20}N_4O_5$	62.85	62.86	6.5	4.76
6	165	70	yellow	$C_{22}H_{20}N_4O_4S$	60.01	60.55	4.9	4.58
7	120	60	yellow red	$C_{26}H_{23}N_5O_3$	68.34	68.87	5.3	5.07
8	166	65	yellow red	$C_{25}H_{23}N_5O$	71.5	73.35	5.9	5.62
9	212	60	yellow	$C_{30}H_{30}N_2O_5$	71.9	72.29	6.0	6.02
10	156	60	pale yellow	$C_{25}H_{22}N_2O_3$	75.2	75.4	6.3	5.53
11	175	65	yellow	$C_{25}H_{20}N_2O_2$	78.8	78.95	5.5	5.26
12	233	70	yellow	$C_{17}H_{16}N_4O$	70.1	69.86	5.7	5.82
13	185	75	yellow	$C_{17}H_{15}N_3O_2$	69.4	69.63	4.9	5.11
14	144	55	yellow	$C_{19}H_{18}N_4O_2$	68.6	68.27	5.53	5.4
15	173	70	orange	$C_{18}H_{17}N_3O_4$	63.9	63.72	5.5	5.02
16	250	65	orange	$C_{18}H_{16}N_3O_3$	67.9	67.68	5.1	4.97
17	189	70	yellow	$C_{18}H_{14}N_2O_3$	70.2	70.59	4.3	4.58
18	170	70	yellow	$C_{18}H_{14}N_2O_4$	67.9	67.88	3.96	4.35
19	165	65	deep yellow	$C_{20}H_{16}N_2O_5$	66.0	65.94	4.3	4.39

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* **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 boild with NaOH (50 ml, 5 N). The precipitated product was coolected and crystallized from ethanol.

Acetion 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 crystallised 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 pricipitated 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_2SO_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.

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