

ORGANIC REACTIONS IN THE AQUEOUS MEDIUM

Part VI. Synthesis of Substituted Pyrazoles and Pyrazolones

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The reactions of semicarbazide hydrochloride and hydrazine monohydrate with ethyl acetoacetate, acetylacetone, benzoylacetone and dibenzoylmethane leading to the formation of pyrazole and pyrazolone derivatives have been intensively studied in the aqueous as well as in the nonaqueous medium under various sets of conditions. This has resulted in the development of simple and convenient methods for the synthesis of pure ethyl acetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III), 3, 5-dimethylpyrazol-1-carboxamide (V), 3, 5-dimethylpyrazole (VI), 3-phenyl-5-methylpyrazole-1-carboxamide (VII), 3-phenyl-5-methylpyrazole (VIII) and 3, 5-diphenylpyrazole (IX). It has been suggested that the reaction of semicarbazide hydrochloride with β -diketo compounds proceeds through four stages. A reaction scheme has been proposed to explain the formation of different products.

Key words. Synthesis, Pyrazole and Pyrazolone derivatives.

Introduction

Hydrazine and hydrazine derivatives react with 1,3-diketo compounds to form pyrrole, pyrazole and pyrazolone derivatives. It has been reported [4-6] that many 3,5-disubstituted pyrazoles possess hypo-glycemic and antimicrobial activity. They are used as corrosion inhibitors, antiflogging agents in photographic systems, and their metal complexes are useful as chemical reagents [7]. The reactions of hydrazine and semicarbazide hydrochloride with β -keto esters and β -diketones leading to the formation of heterocyclic compounds in the pyrazole and pyrazolone series and their methods of preparation have been reported in the literature. The present literature methods [8-16, 18, 21] for the preparation of pyrazole and pyrazolone derivatives involve different steps, and are lengthy and tedious. It was considered appropriate to investigate the reactions of hydrazine and semicarbazide with 1,3-diketo compounds in an attempt to obtain their pyrazole and pyrazolone derivatives particularly in the aqueous medium. The

present work describes the synthesis of compounds (I)- (IX).

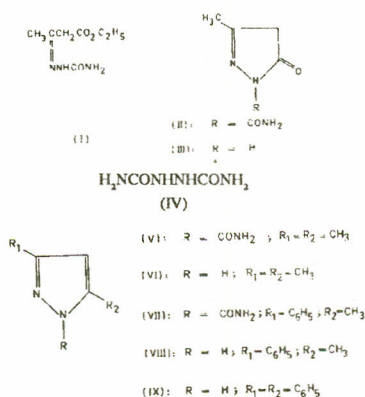
Experimental

General. Experiments were carried out in water, water-solvent systems and in non-aqueous solvents at room temperature ($22 \pm 2^\circ$), below-room temperature in an ice-bath ($5-15^\circ$) and at elevated temperature by heating under mild reflux. The solvents and chemicals used were of analytical grade. Distilled water was used in all the experiments. Since the reaction commenced immediately after the mixing of the reactants, no values of the pH during the condensation could be obtained and only the limits of the prevailing pHs were recorded. The products were isolated by filtration and washed several times with small lots or cold water of solvent mixtures, were dried either in the air or in a vacuum desiccator for 1-3 days. These were purified by recrystallisation from appropriate solvents and identified in the usual way by taking mixture melting points with authentic samples, and confirmed by combustion analysis and IR spectra, which were run on Hitachi Infrared Spectro-photometer (270-30). Every experiment was performed thrice, and their average yields have been reported. The methods for the preparation of the compounds have been described according to the conditions under which the experiments were carried out, and therefore, have been described as follows:

Method (a). At $5-15^\circ$, for 40-60 mins.

Method (b). At $5-15^\circ$, for 5-15 mins., and then leaving the reaction mixtures at room temperature ($24 \pm 2^\circ$) or in a refrigerator ($8-10^\circ$) for 1-4 days.

Method (c). At $5-15^\circ$, for 5-15 min, followed by refluxing for 1-3 hrs.



Compounds synthesised

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REACTIONS OF ETHYL ACETOACETATE WITH SEMICARBAZIDE HYDROCHLORIDE:

Ethyl acetoacetate Semicarbazone (I). Method (a). A solution of semicarbazide hydrochloride (5.58 g; 0.05 mole) was prepared in water (50 ml) and stirred magnetically in an ice-bath until the temperature reached 5-10°. Ethyl acetoacetate (6.50 g; 0.05 mole) was added dropwise with stirring over a period of 10-15 mins. The temperature had a tendency to rise during the addition which was so regulated by external cooling that a temperature of 10-15° was maintained. A white fluffy compound separated immediately after this addition. The reaction mixture was allowed to stand for another 30 mins at the same temperature to complete the precipitation. The compound was filtered at the pump, washed with small lots of cold water till the washings were neutral and, dried in a vacuum desiccator for 2-3 days. The workup afforded (Z)-semicarbazone (I) (5.45g; 58 %). Recrystallisation from ethanol gave white fluffy crystals melting at 128-129°, [8,9] m.p. 128-129°. Its melting point, when mixed with an authentic sample, remained undepressed, and their IR spectra were superimposable. (Found: C, 44.89; H, 6.87; N, 22.44%; $C_7H_{13}N_3O_3$ requires: C, 44.92; H, 6.97; N, 22.46%).

Repeat experiments carried out in 75 and 100 ml of water under similar conditions afforded 4.65 g (50 %) and 4.25 g (46%) of pure semicarbazone (I) respectively.

Reaction carried out by using equimolar quantities (0.05 mole) of ethyl acetoacetate, semicarbazide hydrochloride and sodium hydroxide in 100 ml of water afforded an improved yield (5.75 g, 62%) of (I).

Method (b). Semicarbazide hydrochloride (5.58 g; 0.05 mole), ethyl acetoacetate (6.50 g, 0.05 mole) and sodium hydroxide (2.00 g, 0.05 mole) were dissolved in water (100 ml) and the reaction flask was placed in an ice-bath until the temperature reached 5-10°. After 10-15 min the reaction mixture containing a white compound was allowed to stand at room temperature (24±2°) for 4 days to yield (I) (7.55g; 81%). Recrystallisation from ethanol afforded white fluffy crystals melting at 128-29°.

3-Methylpyrazol-5-one-1-carboxamide (II). Method (b). Semicarbazide hydrochloride (5.58 g; 0.05 mole) and ethyl acetoacetate (6.50 g; 0.05 mole) in 50 ml of water under the conditions as in (b) above afforded a white crystalline compound (II) (3.99g; 56%). It was filtered under mild suction, washed with small lots of cold water and dried in a vacuum desiccator for 2-3 days. Recrystallisation from boiling water afforded white shining crystals melting with decomposition at 194-196°, [14,18] m.p. 194-195°, alone or mixed with an authentic specimen. Their IR spectra overlapped each other. (Found: C, 42.51; H, 4.89; N, 30.02 %; $C_5H_7N_3O_2$ requires; C, 42.55; H, 4.94; N, 29.79%).

3-Methylpyrazole-5-one (III): Hydrazine-1, 2-diamide (IV). Method (c). Semicarbazide hydrochloride (5.58 g; 0.05 mole) was dissolved in water (100 ml) and cooled to 5-10° in an ice-bath. Ethyl acetoacetate (6.50g; 0.05 mole) was added dropwise with good shaking. During the addition the temperature was maintained at 10-15° with external cooling. After 10-15 mins, the flask containing a white fluffy precipitate was equipped with a reflux condenser and transferred to a heating mantle and refluxed gently for 1 hr. At the end of this period the reaction mixture was allowed to cool down to room temperature. Most of the product separated out immediately but for a more complete separation it was cooled in an ice-bath. It was filtered, washed with cold water under mild suction and dried in the air. The yield of the sufficiently pure hydrazine-1, 2-diamide (IV) was 1.10 g (19 %). Further purification was carried out by recrystallisation from boiling water to obtain white shining crystals melting to a clear liquid at 248°, lit. [19] m.p 248°. Its melting point remained undepressed when mixed with an authentic sample, and their IR spectra were identical. (Found; C, 20.37; H, 4.99; N, 47.10 %; $C_2H_6N_4O_2$ requires; C, 20.34; H, 5.08; N, 47.46%).

The combined mother liquor and the washings were evaporated down to 30-40 ml, allowed to cool, and kept overnight in a refrigerator (10-15°) to obtain 3-methylpyrazol-5-one (III) (1.30 g, 27%). Recrystallisation from ethanol afforded white short needles m.p. 222°, lit. [18] m.p 222°. Its melting point remained underpressed when mixed with an authentic sample and their IR spectra were superimposable. (Found: C, 49.02; H, 6.02; N, 28.21 %; $C_4H_6N_2O$ requires; C; 48.98; H, 6.12; N, 28.57 %).

Semicarbazide hydrochloride (5.58 g; 0.05 mole) and ethyl acetoacetate (6.50 g; 0.05 mole) in water (50 ml) were allowed to react first at 5-10° for 10-15 mins and then refluxed for 2-3 hours under the conditions similar to those of the above reaction to yield hydrazine-1, 2-diamide (IV) (1.75 g; 30 %). The reaction in presence of an excess of semicarbazide hydrochloride afforded 2.10 g (37 %) of crude (IV).

REACTIONS OF ACETYLACETONE WITH SEMICARBAZIDE HYDROCHLORIDE :

3, 5-Dimethylpyrazole-1-carboxamide (V). Method (a). Semicarbazide hydrochloride (11.16 g; 0.10 mole) was dissolved in water (100 ml) and cooled to 0-5° in a bath of ice. To this was added acetylacetone (5.0 g; 0.05 mole) gradually with magnetic stirring. During this slow dropwise addition (over a period of 15-20 mins) a white crystalline deposit separated. The reaction mixture was allowed to stand at 5-10° for another 20-30 mins to complete the crystallisation. It was filtered at the pump and washed with small lots of cold water until the washings were neutral. Sufficiently pure (V) (6.12 g; 88%) obtained was further purified by recrystallisation from ethanol

to yield white short needles melting at 112-114°, alone or mixed with an authentic specimen, lit. [15] m.p. 111.4-112.4°. Their IR spectra were identical. (Found: C, 51.82; H, 6.58; N, 29.94%; $C_6H_9N_3O$ requires: C, 51.78; H, 6.47; N, 30.21%).

Reactions carried out by using equimolar quantities of acetylacetone and semicarbazide hydrochloride at molar concentrations of 0.05 mole/litre and 0.10 mole/litre under the conditions similar to those of the above reaction afforded 83% and 37% of (V) respectively.

A repeat experiment carried out by using acetylacetone (5.0 g; 0.05 mole) semicarbazide hydrochloride (5.58 g; 0.05 mole and sodium hydroxide 2.00; 0.05 mole) in water (100 ml) yielded 82% of the product (V).

Method (b). Semicarbazide hydrochloride (5.58 g; 0.05 mole) and acetylacetone (5.0 g; 0.05 mole) in water (100 ml) were allowed to react as in Method (a). The reaction mixture was then kept further for 4 days at room temperature ($24 \pm 2^\circ$) to afford 4.16 g (60%) of white crystals of 3-5-dimethylpyrazole-1-carboxamide (V). This upon recrystallisation from ethanol afforded white short needles melting at 112-114°.

Reaction carried out by using semicarbazide hydrochloride, acetylacetone and sodium hydroxide in equimolar quantities at molar concentration of 0.5 mole/litre yielded 80% of (V).

3, 5-Dimethylpyrazole (VI). Method (c). Semicarbazide hydrochloride (5.58 g; 0.05 mole) was dissolved in water (100 ml) in a round-bottomed flask, and cooled to 0-5° in an ice bath. Acetylacetone (5.0 g; 0.05 mole) was added dropwise with good stirring. During this addition the temperature was maintained at 5-10° with external cooling. After 15-20 mins the flask containing a white crystalline compound was fitted with a reflux condenser and transferred to a heating mantle and refluxed gently for 2 hrs. The mixture was cooled in an ice bath to yield white crystals of (VI) (1.45 g; 30%) It was recrystallised from boiling water to obtain white lustrous crystals, m.p. 107-180°, lit. [20, 21] m.p. 107-108°, alone or mixed with an authentic sample. Their IR spectra were found to be identical. (Found: C, 62.44; H, 8.18; N, 28.79%; $C_5H_8N_2$ requires: C, 62.50; H, 8.33; N, 29.17%).

The above reaction in the presence of an equimolar quantity of sodium hydroxide under similar conditions yielded 26.0% of (VI).

Hydrazine-1, 2-diamide (IV). Semicarbazide hydrochloride (5.58 g; mole) was dissolved in water (100 ml) in a round-bottomed flask, and cooled to 0-5° in an ice-bath. acetylacetone (5.0 g; 0.05 mole) was added slowly with magnetic stirring and the temperature was maintained at 5-10° with external cooling. After 15-20 mins. the flask containing the reaction mixture was transferred to a heating mantle for a gentle reflux for 2-2.5 hrs. It was then allowed to stand at room

temperature ($24 \pm 2^\circ$) for 1 day to yield pure fine crystals (IV) (1.50 g; 25%) melting to a clear liquid at 248-249°.

A lower yield (20) of (IV) was obtained when the above reaction was done in the presence of an equimolar quantity of sodium hydroxide.

REACTIONS OF BENZOYLACETONE WITH SEMICARBAZIDE HYDROCHLORIDE :

3-Phenyl-5-methylpyrazole-1-carboxamide (VII) Method. Benzoylacetone (1.637 g; 0.01 mole) was dissolved in ethanol-water mixture (3:2) (50 ml) by warming slightly. To this was added semicarbazide hydrochloride (2.230 g; 0.02 mole), shaken thoroughly to dissolve and allowed to stand in a refrigerator (8-10°) After 1 day off-white crystalline compound (VII) (1.36 g; 68 %) was filtered at the pump, washed 3-4 times with small lots of cold water and dried in a vacuum desiccator for 2-3 days. The compound was sufficiently pure and did not need further purification. Its melting point (156-157°) remained undepressed when mixed with an authentic sample, lit. [15] m.p. 154-156°, and their IR spectra overlapped each other. (Found: C, 65.72; H, 5.40; N, 20.71%; $C_{11}H_{11}N_3O$ requires: C, 65.67; H, 5.47; N, 20.89%).

3-Phenyl-5-methylpyrazole (VIII). Method. 3-Phenyl-5-methylpyrazole-1-carboxamide (VII) (1.30g) was suspended in water (100 ml) and boiled for 5 mins. The reaction mixture when cooled in ice-cold water yielded pure (VIII) melting at 127-128° alone or mixed with an authentic specimen. [15] m.p. 127-128°. Their IR spectra were also identical. The yield was 0.48 g; 87%. (Found: C, 75.88; H, 6.43; N, 17.50%; $C_{10}H_{10}N_2$ requires: C, 75.95; H, 6.33; N, 17.72%).

REACTIONS OF DIBENZOYLMETHANE WITH SEMICARBAZIDE HYDROCHLORIDE:

3,5-Diphenylpyrazole (IX). Method. Dibenzoylmethane (0.56 g; 0.0025 mole) and semicarbazide hydrochloride (0.558 g; 0.005 mole) were dissolved in ethanol-water mixture (2:1) (120 ml) and allowed to stand at room temperature ($24 \pm 2^\circ$). After 10 days, the reaction mixture was concentrated to about half its original volume by evaporating the solvents on a water bath and kept in a refrigerator (8-10°) for 2-3 hrs. White crystals (0.48 g; 87%) of (IX) obtained were filtered at the pump, washed with ice-cold ethanol-water mixture and dried in the air. Recrystallisation from ethanol-water afforded white needles melting at 200-201°, lit. (15) m.p. 199-200°. Its melting point remained undepressed when mixed with an authentic specimen. Their IR spectra were also identical. (Found: C, 81.74; H, 5.38; N, 12.56%; $C_{15}H_{12}N_2$ requires: C, 81.81; H, 5.45; N, 12.73%).

REACTIONS OF ETHYL ACETOACETATE WITH HYDRAZINE MONOHYDRATE :

3-Methylpyrazole-5-one (III). Method (a). Hydrazine

monohydrate (80%; 6.25 g, 0.01 mole) was dissolved in methanol-water (1:1) mixture (20 ml) and cooled to 0-5° in an ice-bath. To this was added ethyl acetoacetate (13.0 g, 0.10 mole) gradually with magnetic stirring and external cooling to maintain the temperature at 5-10°. After this addition (in 5-20 mins) a white crystalline deposit separated. It was allowed to stand further for 30-40 mins at 5-15° to complete the crystallisation. The compound was filtered at the pump and washed with ice-cold water. Recrystallisation from ethanol gave short needles, melting at 220-222°, lit. [18] m.p. 222°. The yield of the pure compound (III) was 9.15 g; 93 %.

Another 7 experiments were performed under similar conditions, by using equimolar quantities (0.1 mole) of ethyl acetoacetate and hydrazine monohydrate in water (50 ml, 100 ml), methanol (8 ml, 20 ml) ethanol (8 ml, 20 ml) and ethanol-water (1:1) mixture (20 ml). These experiments afforded 68, 53, 84, 62, 74, 59 and 77 % of (III).

Method (b). Hydrazine monohydrate (80 %; 6.25 g, 0.10 mole) was dissolved in water (50 ml) and cooled to 0-5° in an ice-bath. Ethyl acetoacetate (13.0 g; 0.10 mole) was gradually added with magnetic stirring. During this slow dropwise addition (over 15-20 mins) the temperature was maintained at 5-10°. The reaction mixture was then allowed to stand at room temperature (24±2°) for 4 days to yield white crystals (III) (6 g; 68 %) Recrystallisation from ethanol gave short needles m.p. 220-222°.

Method (c). A solution of hydrazine monohydrate (80 %; 6.25g, 0.10 mole) in water (50 ml) was prepared in a round-bottomed flask and cooled to 0-5° in an ice-bath. To this was added ethyl acetoacetate (13.0 g; 0.10 mole) slowly with good shaking, and the temperature was maintained at 5-10°. After the completion of this addition (in 15-20 mins) the flask was fitted with a reflux condenser and transferred to a heating mantle. The mixture was refluxed gently for 1.5 hrs. It was then cooled to room temperature and immersed in ice-cold water to yield a small amount of (III) (0.550g; 6 %). Purification by recrystallisation from ethanol afforded short needles melting at 221-222°.

REACTIONS OF ACETYLACETONE WITH HYDRAZINE MONOHYDRATE

3-5-Dimethylpyrazole (VI). *Method (a).* Hydrazine monohydrate (80%; 15.64 g, 0.25 mole) was dissolved in water (125 ml) and cooled to 0-5° in an ice bath. To this was added acetylacetone (25.0 g, 0.25 mole) dropwise with magnetic stirring. During this addition (in 25-30 mins) the temperature was maintained at 5-15°. The reaction mixture was allowed to stand for another 20-30 mins at the same temperature and white crystals (IV) (11.12 g; 46%) formed were filtered at the pump, washed with cold water and dried in the air. Recrystallisation from boiling water gave white shining crystals melting at 107-108°, literature [20,21] m.p. 107-108°.

Method(b). Acetylacetone (0.25 mole) was added to hydrazine monohydrate (0.25 mole) dissolved in 50 ml of methanol-water mixture (1:1) as in the above experiment and stored in a refrigerator (8-10°). After 1 day white shining flakes (VI) (15.5 g) were obtained. Dilution of the mother liquor with 50 ml of water yielded another crop (1.60 g) of (VI). The total yield of the pure compound was 17.10 g (71%).

Repeat experiments performed in ethanol-water (1:1) mixture, methanol, and ethanol yielded 53, 66, and 57% of (VI).

REACTIONS OF BENZOYLACETONE WITH HYDRAZINE MONOHYDRATE

3-phenyl-5-methylpyrazole (VIII): Method. To benzoylacetone (1.637 g; 0.01 mole) dissolved in ethanol (20 ml) was added hydrazine monohydrate (80%; 1.252 g, 0.02 mole) and refluxed gently for 40-45 mins. The mixture was diluted with 40 ml of water, and refluxed further for 15 mins. At the end of the period the mixture was cooled and immersed in ice-cold water to precipitate out white fluffy compound (VIII) (1.50 g; 96%). It was filtered under mild suction, washed twice with ice-cold water and dried in the air. The filtrate was diluted with 10 ml of water to obtain another crop (0.05 g; 3 %). Recrystallisation from ethanol-water mixture (1:2) afforded fine fluffy needles melting at 127-128°, lit. [15] m.p. 127-128°.

REACTIONS OF DIBENZOYLMETHANE WITH HYDRAZINE MONOHYDRATE

3, 5-Diphenylpyrazole (IX): Method. Dibenzoylmethane (0.561 g; 0.0025 mole) was dissolved in ethanol (15 ml). To this was added hydrazine monohydrate (80%; 0.313 g, 0.005) and the mixture was refluxed gently. After 40-45 mins the reaction mixture was diluted with 5 ml of water and cooled in an ice-bath. White fine crystals (IX) (0.431 g; 78%) precipitated, were filtered at the pump, washed twice with ice-cold ethanol-water mixture and dried in the air. Recrystallisation from ethanol-water (1:2) mixture afforded white needles melting at 200-201° [15] m.p. 199-200°.

Results and Discussion

The reactions of ethyl acetoacetate with semicarbazide hydrochloride at low temperature (5-10°) room temperature (24-2°) and by refluxing in different solvents in varying molar concentrations and at a wide range of pH's (0.90-12.45), developed naturally or by the addition of sodium hydroxide, generally afforded ethylacetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III) and hydrazine-1, 2-diamide (IV). The results are recorded in Table 1. It is obvious from this Table that the maximum yield (81 %) of ethyl acetoacetate semicarbazone (I) was obtained when equimolar quantities of ethyl acetoacetate and semicarbazide hydrochloride in presence of sodium hydroxide were allowed to react under over-all acidic condi-

TABLE 1. REACTIONS OF ETHYL ACETOACETATE WITH SEMICARBAZIDE HYDROCHLORIDE UNDER DIFFERENT PARAMETERS.

S. No.	Medium (ml)	pH Initial-final	Temperature °C	Duration	Products/s	Yield g (%)
<i>Ethyl acetoacetate</i> 0.05 moles (6.50 g)		<i>Semicarbazide hydrochloride</i> 0.05 moles (5.58 g)				
1.	Water (100)	1.15-1.55	5-15	40-45 mins.	(I)	4.25 (46)
2.	" (75)	0.95	"	"	"	4.65 (50)
3.	" (")	0.90	"	"	"	4.45 (58)
4.	" (100)	3.95-4.00*	"	"	"	5.75 (62)
5.	" (")	9.86-12.45**	"	"	Bright yellow solution	
6.	Methanol (")	--	"	"	"	
7.	Ethanol (")	--	"	"	"	
8.	Water (")	1.15-1.55	5-15	20-30 mins.		
			+	+	(II)	2.31 (33)
			24±2	3-4 days		
9.	" (75)	0.95	"	"	"	2.59 (36)
10.	" (50)	0.90	"	"	"	3.99 (56)
11.	" (100)	3.95-4.00*	"	"	(I)	7.55 (81)
12.	Water (100)	9.86-12.45**	5-15	20-30 mins.	Bright yellow solution	
			+	+		
			24±2	3-4 days		
13.	Methanol (")	--	"	"	"	"
14.	Ethanol (")	--	"	"	"	"
15.	Water (")	1.15-1.55	5-15	10-15 mins.	(III)	1.30 (27)
			+	+	+	
			Reflux	1-1.5 hrs.	(IV)	1.10 (19)
16.	" (50)	0.90	5-15	10-15 mins.	(IV)	1.75 (30)
			+	+		
			Reflux	2-3 hrs.		
17.	Water (100)	1.15-1.55	"	"	(IV)	1.67 (28)
18.	" (100)***	--	"	"	"	2.10 (37)
19.	Methanol (100)	--	"	"	Pale yellow solution	
20.	Ethanol (")	--	"	"	--	
<i>Ethyl acetoacetate semicarbazone</i> (1.50 g)						
21.	Water (20)	--	Reflux	15 mins.	(I)	
					+	1.20
					(II)	
22.	" (")	--	"	1 hrs.	(III)	0.12
					+	
					(IV)	0.30
23.	" (")	--	"	3 hrs.	(IV)	0.33

* By the addition of sodium hydroxide 0.05 mole (2.0 g). ** By the addition of sodium hydroxide 0.10 mole (4.0 g). *** By the addition of semicarbazide hydrochloride 0.10 mole (11.16 g)...

tions (pH 3.95-4.00). Under similar conditions these reactants at naturally developed pH (0.90) afforded 3-methylpyrazol-5-one-1-carboxamide (II) (56 %). However, when these reactants were allowed to react at 10-15x for 20-30 mins and then refluxed for 1 hr., a mixture of 3-methylpyrazol-5-one (III) (27 %) and hydrazine-1-, 2-diamide (IV) (19 %) was obtained. Prolonged refluxing resulted in the formation of diamide (IV) (30 %) alone. The same reaction in the presence of an excess of semicarbazide hydrochloride afforded an increased amount (37 %) of (IV). Under the basic conditions (pH 9.86-12.45) no solid product could be obtained. The reactions carried out in non-aqueous media (methanol, ethanol) under all sets of conditions failed to yield any of the above compounds.

The reaction of acetylacetone with semicarbazide hydrochloride yielded 3,5-dimethylpyrazole-1-carboxamide (V), 3,5-dimethylpyrazole (VI) and also hydrazine-1-, 2-diamide (IV). All efforts to get semicarbazone from acetylacetone led to a failure. Maximum yield (88 %) of 3,5-dimethylpyrazole-1-carboxamide (V) was obtained by using acetylacetone and semicarbazide hydrochloride under the conditions spelled out in Table 2. When the reaction mixture, after the addition of acetylacetone to semicarbazide hydrochloride at low temperature (5-10°), was refluxed for 1 hr., it resulted in the formation of a mixture of 3,5-dimethylpyrazole-1-carboxamide (V) and 3,5-dimethylpyrazole (VI). Longer refluxing (2 hrs.) afforded (VI) alone and when the above reaction mixture containing (VI) was allowed to stay at room temperature (24±2°) for 1 day, the reaction proceeded even further to yield hydrazine-1-, 2-diamide (IV).

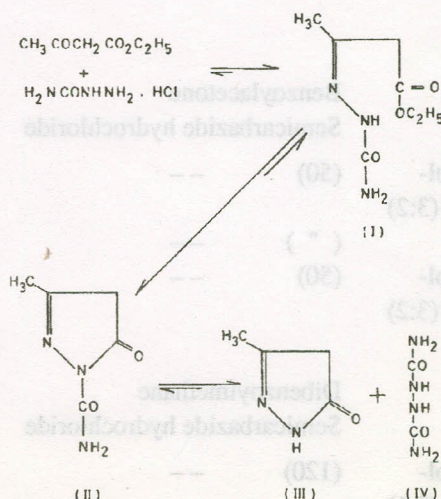
The reactions of benzoylacetone and dibenzoylmethane with semicarbazide hydrochloride were carried out in ethanol water system (Table 2). Benzoylacetone afforded 3-Phenyl-5-methylpyrazole-1-carboxamide (VII) (68%) at 8-10° after 1 day. Efforts to obtain 3-phenyl-5-methylpyrazole (VIII) at a higher temperature resulted in the formation of a crude mixture of (VII) and (VIII). However, sufficiently pure (VIII) could be obtained by boiling (VII) in water for a few minutes. Dibenzoylmethane afforded only 3,5-diphenylpyrazole (IX) (87%) at room temperature (24±2°) after 10 days. At low temperature the reaction failed to commence, and at higher temperatures a diminished yield of crude (IX) was obtained.

The study of the reactions of hydrazine with ethyl acetoacetate, acetylacetone, benzoylacetone, and dibenzoylmethane in the non-aqueous medium as well as in the aqueous non-aqueous mixtures led to the development of simple convenient and economical methods (Table 3) for the preparation of 3-methylpyrazol-5-one (III), 3,5-dimethylpyrazol (VI), 3-phenyl-5-methylpyrazole (VIII) and 3,5-diphenylpyrazole (IX). The reactions of hydrazine monohydrate with ethyl acetoacetate and acetylacetone in methanol-water mix-

tures afford (III) and (VI) in 93 and 71 % yields respectively. Similarly reactions with benzoylacetone and dibenzoylmethane in ethanol-water mixture and ethanol, under very simple conditions give (VIII) 99% and (IX) (78 %). The present literature methods [15, 18, 21] for a just comparable yields are lengthy, tedious and expensive.

It appears from the foregoing discussion that the reaction of ethyl acetoacetate and semicarbazide yields four different products in the aqueous medium. These are ethyl acetoacetate semicarbazone (I), 3-methylpyrazol-5-one-1-carboxamide (II), 3-methylpyrazol-5-one (III) and hydrazine 1, 2-diamide (IV). In case of a similar reaction of semicarbazide with acetylacetone, its semicarbazone could not be isolated while 3,5-dimethylpyrazole-1-carboxamide (V), 3,5-dimethylpyrazole (VI) and the diamide (IV) were obtained. When the reaction was undertaken with benzoylacetone, neither the corresponding semicarbazone nor the diamide (IV) could be isolated. However, 3-phenyl-5-methylpyrazole-1-carboxamide (VII) and 3-phenyl-5-methylpyrazole (VIII) were obtained. The reaction with dibenzoylmethane was only to the formation of 3,5-diphenylpyrazole (IX). Obviously, the reaction of a B-diketo compound processed through four different stages. In the case of ethyl acetoacetate, the reaction is considered to follow the route as shown in the Reaction scheme.

The formation of carboxamide (II) suggests that ethyl acetoacetate yields anti-semicarbazone (I) (w.r.t. methyl group) which later on cyclizes. In analogy with an earlier report [8] this carboxamide (II) readily yields pyrazolone (III). Prolonged refluxing of the carboxamide (II) in the reaction mixture or with additional semicarbazide converts it to a mixture of pyrazolone (III) and diamide (IV) or diamide alone depending upon the conditions (Table 1). This agrees with a similar observation in another reaction [22]. This behaviour of ethyl acetoacetate with semicarbazide suggests that the whole



Reaction Scheme

TABLE 2. REACTIONS OF DIFFERENT β -DIKETONES WITH SEMICARBAZIDE HYDROCHLORIDE UNDER DIFFERENT PARAMETERS.

S. No.	Medium (ml)	pH Initial-Final	Temperature °C	Duration g (%)	Product/s	Yield
			Acetylacetone Semicarbazide hydrochloride		0.05 mole (5.0 g) 0.05 mole (5.58 g)	
1.	Water	(50) 1.17	5-10	40-45 mins	(V)	2.54 (37)
2.	"	(100) 1.65	"	"	"	5.72 (83)
3.	"	(") 7.35 ^b	"	"	"	5.70 (82)
4.	"	(") 10.84 ^{**}	"	"	Pale yellow solution	
5.	"	(") 1.02 ^{**}	"	"	(V)	6.15 (88)
6.	"	(") 1.65	5-10	15-20 mins.	"	4.16 (60)
			+	+		
			24±2	3-4 days		
7.	"	(") 7.35 [*]	"	"	"	5.51 (80)
8.	"	(") 10.84 ^{**}	"	"	Pale yellow solution	
9.	"	(") 1.65	5-10	20-30 mins.	(V)	
			+	+	+	1.34
			Reflux	1-1.5 hrs.	(VI)	(mixture)
10.	Water	(100) 1.65	5-10	20-30 mins.	(VI)	1.45 (30)
			+	+		
			Reflux	2 hrs.		
11.	"	(") "	5-10	20-30 mins.	"	1.50 (25)
			+	+		
			Reflux	2 hrs.		
			+	+		
			24±2	1 days		
12.	"	(") 7.35 [*]	5-10	20-30 mins.	"	1.25 (26)
			+	+		
			Reflux	2 hrs.		
13.	"	(") "	5-10	20-30 mins.	(IV)	1.15 (20)
			+	+		
			24±2	1 day		
14.	"	(") 10.84 ^{**}	5-10	20-30 mins.	Pale yellow solution	
			+	+		
			Reflux	2 hrs.		
			Benzoylacetone Semicarbazide hydrochloride		0.01 mole (1.637 g) 0.02 mole (2.230 g)	
15.	Ethanol- Water (3:2)	(50) --	8-10	1 day	(VII)	1.36 (68)
16.	"	(") --	24±2	4 days	"	1.03 (51)
17.	Ethanol- Water (3:2)	(50) --	Reflux	45-60 mins	(VII)	1.01 g
			+	+	+	(mixture)
			8-10	1 day	(VIII)	
			Dibenzoylmethane Semicarbazide hydrochloride		0.0025 mole (0.561 g) 0.005 mole (0.558 g)	
18.	Ethanol- Water (2:1)	(120) --	8-10	1 day	Pale yellow solution	

(Cont'd...)

(Table 2 continue...)

19.	"	(")	--	24±2 + Reflux + 8-10	10 days + to concentrate + 2-3 hrs.	(IX)	0.48 (87)
20.	"	(")	--	Reflux	1-1.25 hrs.	"	0.33 (60) (crude)
				3, 5-Dimethylpyrazole-1-carboxamide (V)	1.30 g		
21.	"	(50)	--	Reflux	25-30 mins.	(VI)	0.55 (62)
22.	"	(")	--	"	40-45 mins.	(IV)	0.14 (26)
				3-Phenyl-5-methylpyrazole-1-carboxamide (VII) (1.30 g)			
23.	"	(100)	--	Boil	5 mins.	(VIII)	0.67 (68)

* By the addition of sodium hydroxide 005 mole (20 g). ** By the addition of sodium hydroxide 010 mole (40 g). *** Semicarbazide hydrochloride 010 mole (1116 g).

TABLE 3. REACTIONS OF DIFFERENT β -DIKETONES/ β -KETO ESTER WITH HYDRAZINE MONOHYDRATE UNDER DIFFERENT PARAMETERS.

S No.	Medium	(ml)	Temperature °C	Duration	Product/s	Yield g (%)
				0.10 mole (130 g)		
				Hydraine monohydrate	0.10 mole (80%, 625 g)	
1.	Water	(100)	5-15	45-60 mins.	(III)	5.20 (53)
2.	"	(50)	"	"	"	6.65 (68)
3.	Methanol	(20)	"	"	"	6.10 (62)
4.	"	(8)	"	"	"	8.24 (84)
5.	Ethanol	(20)	"	"	"	5.83 (59)
6.	"	(8)	"	"	"	7.28 (74)
7.	Methanol	(20)	"	"	"	9.15 (93)
		-Water	(1:1)			
9.	Water	(50)	5-15 + 24±2	15-20 mins. + 4 days.	"	6.68 (68) (crude)
10.	Water	(50)	5-15 + Reflux	15-20 mins. + 1 hrs.	(III)	0.55 (6) (crude)
				0.25 mole (25 g)		
				Hydrazine monohydrate	0.25 mole (80%, 15.64 g)	
11.	Water	(125)	5-15	45-60 mins.	(VI)	11.12 (46)
12.	Methanol	(20)	5-15 + 8-10	20-30 mins. + 1 day	"	15.80 (66)
13.	Ethanol	(20)	"	"	"	13.74 (57)
14.	Methanol-	(50)	"	"	"	17.10 (71)
		Water	(1:1)			
15.	Ethanol	(50)	"	"	"	12.80 (53)

(Contd.....)

(Table 3 continue.....)

			Benzoylacetone	0.01 mole (1.637 g)		
			Hydraine monohydrate	0.02 mole (80%, 1.2552 g)		
16.	Ethanol -Water	(60) (1:2)	Reflux	55-60 mins.	(VIII)	1.55 (99)
			Dibenzoylmethane	0.0025 mole (0.561 g).		
			Hydraine monohydrate	0.005 mole (80%, 0.313 g)		
17.	Ethanol	(15)	Reflux	40-45 mins.	(IX)	0.431 (78)

reaction involves equilibrium. However, the backward reaction is assumed to be slower since the additionally added semicarbazide, no doubt, increases the yield of the diamide (IV) but not significantly (Table 1). Moreover, 3,5-Dimethylpyrazole-1-carboxamide (V when refluxed in water for about 30 mins, yields 3,5-dimethylpyrazole (VI). However, Prolonged refluxing ends up with the formation of the diamide (IV) alone (Table 2). This observation substantiates the possibility of a reversible reaction. The semicarbazones of acetylacetone, benzoylacetone, and dibenzoylmethane could not be isolated. Thus, benzoylacetone directly affords pyrazole carboxamide (VII) and finally the pyrazole (VIII). In case of dibenzoylmethane the reaction proceeds so rapidly that it affords only the corresponding pyrazole (IX).

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