

Physical Sciences Section

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ORGANIC REACTIONS IN AQUEOUS SOLUTION

Part I. Influence of Various Parameters on the Reaction of Ethyl Acetoacetate and Hydroxylamine Hydrochloride in the Formation of 2,2-Di(3-Methylisoxazol-5-one-4-yl) Propane, 3-Methylisoxazol-5-one Anhydride and 4-Isopropylidene-3-Methylisoxazol-5-one

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The reaction of ethyl acetoacetate and hydroxylamine hydrochloride has been thoroughly investigated particularly in the aqueous medium. Effects of variations of parameters like molar concentration, molar ratio, pH changes and temperature variation have been studied. Optimum conditions for the formation of 4-isopropylidene-3-methylisoxazol-5-one, 3-methylisoxazol-5-one anhydride and 2,2-di(3-methylisoxazol-5-one-4-yl) propane have been determined. The maximum yields of these compounds were 67.3, 57.5 and 63.0 % respectively. A possible mechanism for the formation of these compounds has also been suggested.

Key words: Synthesis, Isoxazolones, Derivatives.

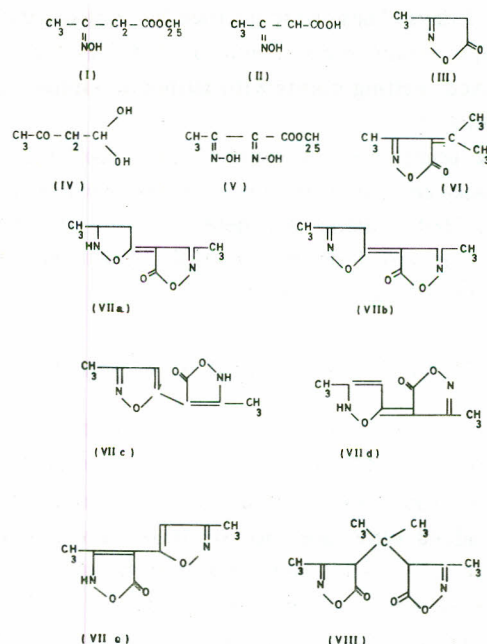
INTRODUCTION

The reaction of ethyl acetoacetate with hydroxylamine was first studied by Westenberger [1]. He reported the formation of (I). The hydrolysis of this compound yielded (II). Hantzsch [2] investigated this reaction thoroughly and reported the formation of (III). He obtained (IV) from ethyl acetoacetate and ammoniacal hydroxylamine. Hantzsch [2] repeated the reaction under the conditions given by Westenberger [1] and obtained an oily compound (I) which yielded (II) on hydrolysis. The oxime (I) and dioxime (V) were also reported [3,4]. The synthesis of 4-isopropylidene-3-methylisoxazol-5-one (VI) was reported by Schiff and Betti[5].

Knorr and Reuter [6] prepared a product with physical properties identical to the compound reported by Hantzsch [2] named by him as methylisoxazolone. Uhlenhuth [7] prepared a number of salts and alkyl derivatives of this compound and he suggested that "methylisoxazolone" as prepared by Hantzsch [2] might be "dimolecular". A molecular weight determination made by Uhlenhuth [7] agreed well with a dimolecular structure of some sort. Donleavy and Gilbert [8] synthesized this substance according to the method of Hantzsch [2] and found it to correspond exactly to (VII_a). In later publications Khromov and Porai-Koshits [9-12] reported not only a method of preparation for this compound, but also designated this as 3-methylisoxazol-5-one anhydride (VII_b).

Katritzky, Oksne and Boulton [13] prepared methylisoxazol-5-one (III) from its morpholine salt, further

reaction of which yielded (VII_a) [14]. Jacques and others [15] obtained (III) and (VII_c) under alkaline conditions. Nishiwaki [16] observed that the reaction of ethyl acetoacetate and hydroxylamine generally afforded (VII_b) but in alkaline conditions it gave exclusively a compound C₁₁H₁₄N₂O₄ (VIII). Schulz [17] also prepared (III) and (VII_b). Gosh and Chaudhry [18] reported that the condensation of hydroxylamine with ethyl acetoacetate yielded dimethylisoxazole (VII_e).



Products from ethyl acetoacetate and hydroxylamine.

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After looking into the details of the investigations of almost all the previous researchers, one finds them quite conflicting. It, thus, necessitates the reinvestigation of this reaction to determine the different parameters which are likely to affect the formation of the products. This paper describes the reaction of ethyl acetoacetate and hydroxylamine particularly, in an aqueous medium under different temperatures, mole concentrations, molar ratios, simple catalysts (acid or alkalis) and a wide range of pH. It is, therefore, an attempt to find suitable parameters for the synthesis of compounds (VI), (VII and VIII).

EXPERIMENTAL

General. Experiments at room temperature ($20 \pm 2^\circ$) and lower temperature ($10 \pm 2^\circ$) were performed in stoppered flasks. Experiments in non-aqueous media (solvent), were carried out in quickfit glass apparatus by heating under mild reflux. The solvents and chemicals used were either of analytical grade or were purified by distillation or recrystallization just before use. Distilled water was used in all the experiments and pH's were recorded by noting the natural pH of the reaction mixture as soon as it became homogeneous or soon after the addition of acid or alkali. Since the reaction commenced after mixing of the reactants, no values of the pH during the condensation could be obtained and only the limits of the probable prevailing pH were recorded by taking the pH of the mother-liquor at the end of the reaction. The products formed were isolated by filtration and, after washing with a small amount of water, were dried at room temperature in a vacuum desiccator for 2-3 days. These were purified by recrystallization from the appropriate solvents and identified in the usual way by mixed melting points with authentic samples confirmed by analysis.

Melting points were determined on a Kofler microscope hot stage and are uncorrected and pH's were recorded on a Hanna H8417 digital pH meter. Infrared absorption spectra were recorded on Beckman-IR 5A and Beckman Acculab-10 infrared spectrometers.

Reaction 1.

2,2-Di(3-methylisoxazol-5-one-4-yl) propane (VIII).

Methods. (a) To each of seven flasks containing hydroxylamine hydrochloride (0.05 mole; 3.475 g) dissolved in 25, 37.5, 50, 100, 200, 250 and 500 ml of water respectively was added ethyl acetoacetate (0.05 mole; 6.50 g) without external cooking, and shaken gently to dissolve. It was allowed to stand at room temperature ($20 \pm 2^\circ$). The reaction mixtures became pale yellow after a few hours. Pale yellow crystals began to appear in the first four flasks

after 2 days. In the fifth flask, however, the reaction was rather slow and the formation of crystals started after 13 days. After 15 days the precipitate of (VIII) in decreasing amounts (2.50 g; 63.0 %) (2.40 g; 60.6 %), (2.30 g; 57.9 %), (1.70 g; 42.9 %) and (0.20 g; 5.1 %) were obtained from the first five flasks. No solid product formed in the last two flasks even after standing for 240 days (Table 1). The precipitate on recrystallization from ethanol afforded colourless crystals, m.p. $106-107^\circ$, (lit. [16] m.p. $106-107^\circ$) which turned light orange on standing. Its mixed melting point with an authentic sample remained undepressed.

(b) The above experiment was repeated at $10 \pm 2^\circ$ using equimolar amounts (0.05 mole) of hydroxylamine hydrochloride (3.475 g) and ethyl acetoacetate (6.5 g) taken in water (50 ml). After 10 days off-white crystals (0.35 g) were obtained which on recrystallization from ethanol afforded colourless rods of (VIII). The mother-liquor on further standing yielded six additional crops (0.62, 0.42, 0.33, 0.31, 0.25 and 0.08) collected after every 20 days. combined crops of crystals (2.36 g; 59.4 %) were purified from ethanol (Table 1).

(c) To hydroxylamine hydrochloride (0.10 mole; 6.95 g) dissolved in water (50 ml) was added hydrochloric acid (0.10 mole in 25 ml of water) followed by ethyl acetoacetate (0.10 mole; 13.0 g). It was allowed to stand at $10 \pm 2^\circ$ with occasional shaking. Off-white crystals (1.21 g) formed after 20 days were filtered. Recrystallization from ethanol afforded colourless rods (VIII). The bright orange filtrate on further standing yielded another two crops (1.48 and 1.20 g) of the same compound after 30 and 60 days. The total amount of (VIII) (3.89 g; 49 %) was obtained in this experiment which lasted 110 days.

(d) To hydroxylamine hydrochloride (0.10 mole; 6.95 g) dissolved in water (50 ml) was added sodium hydroxide (0.15 mole; 6.0 g dissolved in 25 ml of water) followed by ethyl acetoacetate (0.10 mole; 13.0 g) and allowed to stand at $10 \pm 2^\circ$ with occasional shaking. The reaction mixture soon became homogeneous, turned yellow and then orange after 30 minutes. After 20 days white crystals (0.45 g; 5.8 %) were obtained and recrystallized from ethanol to yield colourless rods (VIII) m.p. $106-107^\circ$.

No more solid product separated even when the reaction mixture was allowed to stand for another 40 days.

(e) Hydroxylamine hydrochloride (0.10 mole; 0.95 g) in water (50 ml) was treated with sodium hydroxide (0.20 mole; 8.0 g) dissolved in water (25 ml). To this was added ethyl acetoacetate (0.10 mole; 13.0 g), shaken gently till a clear solution was obtained and allowed to stand at $10 \pm$

2°. It was pale yellow 30 minutes later. After standing 30 days, hydrochloric acid (0.20 mole) was added to yield pale yellow crystals (VIII) (1.46 g) after 10 days. Recrystallization afforded white crystals melting at 106-107°. The yellowish orange mother-liquor on longer standing yielded further three crops of (VIII) (1.90, 1.10 and 0.50 g) after 30, 60 and 110 days respectively. Thus the total of compound (VIII) (4.96 g; 63 %) was obtained in this reaction over a period of 140 days.

(f) Reaction carried out using ethyl acetoacetate (0.10 mole; 13.0 g) hydroxylamine hydrochloride (0.10 mole; 6.95 g), morpholine (0.20 mole) and hydrochloric acid (0.20 mole) in 75 ml of water under the conditions similar to those of reaction (a) yielded (VIII) (2.1 g) after 50 days, on further standing for another 30 days the filtrate yielded another crop (VIII) (1.15 g), m.p. 1-6-107°. A total of 3.25 g (41 %) was obtained from this reaction mixture after 80 days.

(g) Ethyl acetoacetate (0.10 mole; 13.0 g) was gradually added to a solution to hydroxylamine hydrochloride (0.10 mole; 6.95 g) in aqueous sodium hydroxide (0.22 mole; 8.80 g dissolved in 500 ml of water) cooled to about 10°. It was allowed to stand at 10 ± 2° with occasional shaking and, after 5 days, hydrochloric acid (0.20 mole) was added to this pale yellow reaction mixture and allowed to stand further. After 20 days pale yellow crystals (VIII) (1.25 g) were filtered which on recrystallization from ethanol gave colourless crystal, m.p. 106-107°. On longer standing (70 days) the filtrate afforded another crop (VIII) (2.10 g) m.p. 106-107°. This experiment yield a total of 3.35 g (42.2 %) of (VIII).

Reaction II.

3-Methyl-4-(3-methylisoxazol-5-one)-isoxazol-5-one
(3-Methylisoxazol-5-one anhydride) (VII)

Methods. (a) Ethyl acetoacetate (0.10 mole; 13.0 g) was gradually added to a solution of hydroxylamine hydrochloride (0.10 mole; 6.95 g) in aqueous sodium hydroxide (0.33 mole; 13.20 g dissolved in 500 ml of water) cooled to about 10° and the mixture was allowed to stand at 10 ± 2° with occasional shaking. After 5 days when the reaction mixture was a clear light yellow solution, hydrochloric acid (0.3 mole) was added and the mixture allowed to stand further. After 70 days an additional amount of hydrochloric acid (0.05 mole) was added to the dark brown reaction mixture to precipitate a pale yellow fluffy compound (VII) (5.20 g; 57.8 %) which on recrystallization afforded pale yellow needles melting at 169-170° with decomposition, alone and mixed with an authentic specimen, lit. (2,7) m.p. 169-70°.

(b) To a solution of hydroxylamine hydrochloride (0.1 mole; 6.95 g) in aqueous sodium hydroxide (0.11 mole; 4.4 g dissolved in 100 ml of water) and cooled to about 10°, was gradually added ethyl acetoacetate (0.1 mole; 13.0 g). It soon became homogeneous on shaking. This yellowish orange solution was allowed to stand at 10 ± 2°, when after 5 days the reaction mixture was dark brown. Fine pale yellow needles (VII) (1.47 g) formed after 10 days and were filtered off. The filtrate was again allowed to stand at 10 ± 2° and yielded (VIII) (1.60 g) after 40 days and (VII) (0.40 g) after another 20 days. To this dark brown sirupy mother-liquor was added a further quantity of sodium hydroxide (0.11 mole; 4.4 g), shaken vigorously to dissolve followed by addition of hydrochloric acid (0.2 mole) after 6 days. A pale yellow fluffy precipitate appeared immediately, and was allowed to settle for a day and was then filtered off to yield (VII) (1.68 g). Recrystallization of (VIII) from ethanol yielded white crystals m.p. 106-107° which on standing acquired an orange tinge. Recrystallization of (VII) afforded white long silky needles from ethanol-water (1:2) melting at 169-70° with decomposition.

(c) To a solution of hydroxylamine hydrochloride (0.1 mole; 6.95 g) in aqueous sodium hydroxide (0.11 mole; 4.4 g dissolved in 500 ml of water) cooled to about 10°, was gradually added ethyl acetoacetate (0.1 mole; 13.0 g). The reaction mixture on thorough shaking became homogeneous and was allowed to stand at 10 ± 2°. It was yellow after 1 hour and turned reddish brown after 60 days, when pale yellow needles (VII) (1.35 g) separated and were filtered off. To the mother-liquor was added a further quantity of sodium hydroxide (0.11 mole; 4.4 g), shaken vigorously to dissolve, followed by acidification with hydrochloric acid (0.2 mole) after 6 days. A fluffy precipitate formed immediately. This additional crop (VII) (1.65 g), removed after 1 day, on recrystallization from ethanol-water (1:2) afforded white long silky needles melting at 169-70° with decomposition. The overall yield of (VII) after 66 days was (3.0 g 33.3 %), while identical experiment when performed at temperature 20 ± 2° yielded two crops (1.9 g; after 60 days and additional 1.02 g, after another six days totalling 2.92 g; 32.4 %).

Reaction III.

4-Isopropylidene-3-methylisoxazol-5-one (VI)

Methods. (a) Ethyl acetoacetate (0.5 mole; 6.50 g) was gradually added to a solution of hydroxylamine hydrochloride (0.10 mole; 6.95 g dissolved in 50 ml of water) and shaken thoroughly till homogeneous. It was allowed to stand at

$10 \pm 2^\circ$ with occasional shaking. After 50 days crystalline powder (0.95 g) filtered off which on recrystallization gave colourless rods (VIII) m.p. $106-107^\circ$. Longer standing yielded two successive crops (0.35 g and 0.25 g) of crude (VI) which on purification gave long needles melting at $120-121^\circ$ lit. (5,16 m.p. $120-121^\circ$). When mixed with an authentic specimen its melting point remained undepressed.

The experiment when repeated at room temperature $20 \pm 2^\circ$ gave (VIII) (0.63 g) after the reaction mixture had stayed 15 days, and 10 days later (VI) (0.35 g) was also collected.

(b) Ethyl acetoacetate (0.10 mole; 13.0 g) was gradually added to a solution of hydroxylamine hydrochloride (0.05 mole; 3.475 g dissolved in 50 ml of water) and shaken thoroughly till homogeneous. It was allowed to stand at $10 \pm 2^\circ$ with occasional shaking. After 10 days off-white crystals (VIII) (1.00 g) were obtained which on recrystallization from ethanol afforded colourless rods, m.p. $106-107^\circ$. The yellow mother liquor on further standing for 20 days yielded pale yellow needles (VI) (3.15 g). Recrystallization from ethanol afforded colourless needles melting at $120-121^\circ$. An additional crop of (VI) (1.20 g) was collected after another 20 days. Yield of (VI) was 4.35 g; 62.6 %.

A repeat experiment was carried out at room temperature $20 \pm 2^\circ$, which after three days afforded (VIII) (3.35 g), and after six days also yielded (VI) (0.33 g).

(c) Ethyl acetoacetate (0.1 mole; 13.0 g) was added gradually to a solution of hydroxylamine hydrochloride (0.1 mole; 6.95 g) in aqueous sodium hydroxide (0.11 mole; 4.4 g dissolved in 250 ml of water) cooled to about 10° . The reaction mixture soon became homogeneous on shaking and became yellow. It was allowed to stand at $10 \pm 2^\circ$ when it turned brown after 5 days. After 60 days yellow shining needles (VI) (2.48 g), separated and were filtered off. Recrystallization from ethanol gave pale yellow needles melting at $120-121^\circ$. To the dark brown mother liquor was added a further quantity of sodium hydroxide (0.11 mole; 4.4 g) and shaken vigorously to dissolve. It was acidified with hydrochloric acid after 6 days. Pale yellow fluffy needles (VII) (1.68 g) formed immediately and were removed after 1 day. Recrystallization afforded long white needles melting with decomposition at $169-170^\circ$.

(d) To hydroxylamine hydrochloride (0.10 mole; 6.95 g) dissolved in water (50 ml) was added sodium hydroxide (0.10 mole; 4.0 g dissolved in 25 ml of water) followed by ethyl acetoacetate (0.10 mole; 13.0 g). It was allowed to stand for 60 days at $10 \pm 2^\circ$ with occasional shaking. The turbid reaction mixture was yellow in the

beginning, orange after 15 minutes, a light brown solution after 7 days and turned dark brown towards the end of the reaction. It yielded Compound (VIII) (0.65 g) after 20 days, compound (VI) (2.80 g) after 30 days and compound (VII) (1.30 g) after 60 days. Purification of (VIII) from ethanol gave colourless rods m.p. $106-107^\circ$, (VII) from ethanol water (2:1) long silky needles melting at $169-170^\circ$, and (VI) from ethanol afforded needles m.p. $120-121^\circ$.

(e) Hydroxylamine hydrochloride (0.10 mole; 6.95 g), sodium hydroxide (0.20 mole; 8.0 g) and ethyl acetoacetate (0.10 mole; 13.0 g) were dissolved in 500 ml of water to form a clear solution. It was kept at $10 \pm 2^\circ$ for 30 days before hydrochloric acid (0.20 mole) was added. The pale yellow colour of the solution darkened to yellowish orange. After 50 days compound (VI) (1.25 g) formed and was collected. Mother-liquor after 20 days yielded more of (VI) (1.00 g). This experiment yielded a total of 2.25 g of (VI) after 70 days. This on recrystallization from ethanol afforded pale yellow lustrous needles melting at $120-121^\circ$.

(f) Ethyl acetoacetate (0.10 mole; 13 g) and hydroxylamine hydrochloride (0.10 mole; 6.95 g) in acetone (100 ml) were taken in a stoppered flask and allowed to stand at room temperature ($20 \pm 2^\circ$). After 10 days the light yellow solution was transferred to a china dish and kept in a fume cupboard for the acetone to evaporate at room temperature. After 30 days a mixture of crystalline mass and a small quantity of dark red oil was obtained. It was washed with water to give sufficiently pure crystals of (VI) (2.5 g; 36.0 %) m.p. $120-121^\circ$. Yield of (VI) in methanol under similar conditions was 4.68 g (67.3 %).

(g) Ethyl acetoacetate (0.10 mole; 13.0 g), hydroxylamine hydrochloride (0.10 mole; 6.95 g) and acetone (100 ml) were heated under gentle reflux. The mixture became homogeneous and formed a light yellow solution after 2 hours. After 6 hours, acetone was distilled off and the residue, a mixture of crystalline mass and dark red oil, was washed with a small quantity of water to give light orange crystals (1.90 g; 27.3 %) which on purification by recrystallization from ethanol yielded colourless needles (VI) m.p. $120-121^\circ$.

The reaction carried out in methanol under similar conditions yielded (2.24 g; 32.2 %) of the same compound (VI).

RESULTS AND DISCUSSION

The reactions of ethyl acetoacetate and hydroxylamine hydrochloride in equimolar quantities in varying concentrations in the aqueous medium at room temperature ($20 \pm 2^\circ$) with molar concentrations varying from 0.10 to 2 moles/litre Table 1 yielded (VIII). After fifteen days

the maximum yield (2.5 g; 63.0 %) was obtained at a concentration of 2 moles/litre and pH 0.20-0.25. It gradually decreased to a minimum (0.20 g; 5.1 %) at a concentration of 0.25 moles/litre (pH 0.70-1.30). The filtrate set aside for further observation yielded no additional crops. Concentration lower than this failed to yield any precipitate. The reaction at lower temperature ($10 \pm 2^\circ$) using equimolar concentration of the reactants proceeded at a much slower rate, as expected, with a slightly higher yield of (VIII) (59.4 as against 57.9 % at $20 \pm 2^\circ$), at a molar concentration of 1 mole/litre but only after a lapse of 130 days, Table 1.

The reaction further studied by varying the molar ratios of the reactants at $10 \pm 2^\circ$ showed that when ethyl acetoacetate was treated with an excess of hydroxylamine hydrochloride in the molar ratio 1:2 respectively, the reaction proceeded slowly to yield impure (VIII) (0.95 g) after 50 days. The filtrate, after another 40 days, gave (VI) (0.61 g) of low purity. However, at room temperature ($20 \pm 2^\circ$) the reaction was faster and after 15 days (VIII) (0.63 g) was obtained and 10 days later, (VI) (0.35 g) was also separated Table 3.

However, in an excess of ethyl acetoacetate in the molar ratio 2:1 the rate of reaction was comparatively faster even at $10 \pm 2^\circ$ and after 10 days (VIII) (1.0 g) separated out, and the mother liquor after 40 days afforded sufficiently pure compound (VI) (4.35 g) in 62.5 % yield Table III. This reaction at room temperature ($20 \pm 2^\circ$) yielded (VIII) (3.35 g), while (VI) was only 0.33 g. The yield of compound (VIII) was higher at room temperature ($20 \pm 2^\circ$) as compared with its yield at lower temperature ($10 \pm 2^\circ$).

Equimolar quantities of ethyl acetoacetate and hydroxylamine hydrochloride in the presence of a mole of hydrochloric acid pH ≤ 0 gave (VIII) in 49 % yield Table 1. In the presence of an equivalent amount of sodium hydroxide (pH 3.46-3.11) it yielded crops of (VIII) (0.65 g), (VI) (2.8 g) and (VII) (1.30 g) after 20, 30 and 60 days respectively Table 3. A slight excess of sodium hydroxide pH 5.44-6.93 gave a small amount of only (VIII) (5.8 %) (Table 1).

A mixture of ethyl acetoacetate and hydroxylamine hydrochloride at a molar concentration of 1.33 moles/litre in the presence of sodium hydroxide (pH 11.34) yielded no precipitate even after 30 days. Acidification of this reaction mixture with hydrochloric acid yield (VIII) (63 %) after another 110 days. Reaction in morpholine (pH 8.44) gave (VIII) in 41.0 % yield Table 1. A dilute mixture (0.2 moles/litre) in the presence of the same amount of sodium hydroxide (pH 10.6) under similar

conditions afforded (VI) (32.4 %) Table 3. At the same molar concentration of ethyl acetoacetate and hydroxylamine hydrochloride (0.2 moles/litre) containing a slightly increased amount of sodium hydroxide (pH 12.1), followed by acidification with hydrochloric acid (after 5 days) yielded (VIII) (42.2 %) after 70 days Table 1. Excess of alkali (pH 13.2) afforded (VII) (57.8 %) immediately after strong acidification Table 2.

Reactions using molar concentrations of ethyl acetoacetate and hydroxylamine hydrochloride varying from 1 to 0.20 moles/litre in presence of a calculated amount of sodium hydroxide so that the conditions prevailing were still acidic, (pH 2.81-4.75) gave (VI), (VII) and (VIII) in varying amounts after a reaction period of 60 days Table 2, 3. However, when reaction mixtures or mother-liquors were made strongly alkaline by adding further quantities of sodium hydroxide (pH 13) the anhydride (VII) precipitated exclusively on acidification of the reaction mixture or the mother liquor Table 2, 3.

The reaction of ethyl acetoacetate with hydroxylamine hydrochloride in acetone and methanol at room temperature $20 \pm 2^\circ$ and under mild reflux led to the formation of (VI) in varying yields Table 3. However, the maximum yield of (VI) (67.3 %) was obtained by carrying out the reaction in methanol (room temperature) and the minimum (27.3 %) in acetone. Refluxing in higher boiling solvents (ethanol, benzene and also in water) resulted in the formation of crude dark red oil and a small amount of a solid material. This was probably a mixture of the oxime of ester, methylisoxazol-5-one and decomposition products with unreacted ester and amine. The mixture was soluble in water and most other solvents and could not be purified by distillation without decomposition. Therefore, it was discarded without further investigation Table 3.

CONCLUSION

The reaction of ethyl acetoacetate with Hydroxylamine at room or below room temperatures generally affords three compounds (VI), (VII) and (VIII), which contradicts an earliest report [16] Tables 1, 2 and 3.

Equimolar quantities of hydroxylamine hydrochloride and ethyl acetoacetate generally affords (VIII). A reasonable amount of this compound is obtained at room temperature ($20 \pm 2^\circ$) when the concentration of ethyl acetoacetate and hydroxylamine hydrochloride is 1-2 moles/litre and pH of reaction mixture is 0.12-0.40. This contradicts an earlier report by Nishiwaki [16] according to which this compound is obtained in the alkaline medium. Lower temperature ($10 \pm 2^\circ$) decreases the yield as well as the rate of reaction Table 1.

Table 1. Parameters affecting the synthesis of 2,2-di(3-methylisoxazol-5-one-4-yl) propane (VIII) from ethyl acetoacetate and hydroxylamine hydrochloride.

	Molar concentration (moles/litre)	pH	Temperature °C	Duration (day)	Yield g(%)
		Initial-final			
(a)	2.00	0.20–0.25	20 ± 2	15	2.50(63.0)
	1.33	0.25–0.40	"	"	2.40(60.6)
	1.00	0.30–0.55	"	"	2.30(57.9)
	0.50	0.50–0.99	"	15	1.70(42.9)
	0.25	0.70–1.30	"	"	0.20(5.1)
	0.20	0.90–1.34	"	—	—
	0.10	1.00–1.60	"	—	—
(b)	1.00	0.30–0.55	10 ± 2	110	2.28(57.4)
	"	"	"	140	2.36(59.4)
(c)	1.33	"	"	20	1.21
	"	"	"	30	1.48
	"	"	"	60(110)	1.20(3.89;49.5)
(d)	1.33	5.44–6.93	"	20	0.45(5.8)
	"	"	"	30	—
	"	"	"	60	—
(e)	1.33	11.34(0.12 after 30 days)	"	140	4.96(63.0)
(f)	"	8.44(0.50 after 30 days)	"	80	3.25(41.0)
(g)	0.20	12.1 (1.29 after 5 days)	"	70	3.55 (42.2)

Table 2. Parameters affecting the formation of 3-methylisoxazol-5-one anhydride (VII) from ethyl acetoacetate and hydroxylamine hydrochloride.

	Molar concentration (moles/litre)	pH	Temperature °C	Duration (days)	Yield g(%)
		Initial-final			
(a)	0.20	13.2	10 ± 2	—	—
	"	4.78(after 5 days)	"	—	—
	"	2.29(After 70 days)	"	70	5.20(57.8)
(b)	1.00	2.81	"	10	1.47
	"	"	"	40	1.60(VIII)
	"	"	"	60	0.40
	"	13.20(after 60 days)	"	—	—
	"	0.72(after 66 days)	"	66	1.68(39.4)
(c)	0.20	4.75	10 ± 2	60	1.35
	"	"	"	66	1.65(33.3)
	"	13.07	"	—	—
	"	1.29(after 66 days)	20 ± 2	66	1.90
	"	"	"	66	1.02(32.4)

Table 3. Parameters affecting the formation of 4-isopropylidene-3-methylisoxazol-5-one (VI) from ethyl acetoacetate hydroxylamine hydrochloride.

	Molar ratios (ester; amine)	pH	Temperature °C	Duration (days)	Yield g(%)
		Initial-final			
(a)	1:2	0.50-0.18	10±2	50	0.95 (VIII)
	"	"	"	90	0.61
	"	"	20±2	15	0.63 (VIII)
	"	"	"	25	0.35
(b)	2:1	0.66-0.32	10±2	10	1.00(VIII)
	"	"	"	50	4.35(62.6)
	"	"	20±2	3	3.35(VIII)
	"	"	"	6	0.33
Molar concentration (Ester & amine)					
(c)	0.40	3.67	10±2	60	2.48(35.7)
	"	13.10(after 60 days)	"	—	—
	"	1.00(after 66 days)	"	66	1.68(VII)
(d)	1.33	3.46-3.11	"	20	0.65(VIII)
	"	"	"	30	2.80(403)
	"	"	"	60	1.30(VII)
(e)	0.20	10.60	10±2	70	2.25(32.4)
		1.12(after 30 days)			
(f)	1.00 (in acetone)	—	20±2	—	2.50(36.0)
	1.00 (in methanol)	—	"	—	4.68(67.3)
(g)	1.00 (in acetone)	—	reflux	—	1.90(27.3)
	1.00 (in methanol)	—		—	2.24(32.2)

Lowering of pH by the addition of hydrochloric acid decreases the yield of (VIII). Weakly acidic conditions (pH 3.11-3.46) made by the addition of an equivalent amount of an alkali (sodium hydroxide) further decreases the yield of (VIII) and favours the formation of (VI) and (VII). Nearly neutral conditions (pH 5.44-6.93) made by the addition of excess of sodium hydroxide gives only a small amount of (VIII) Table 2.

When ethyl acetoacetate and hydroxylamine are not used in equimolar quantities, a mixture of (VI) and (VIII) is obtained, excess of ethyl acetoacetate favours the formation of (VI) Table 2.

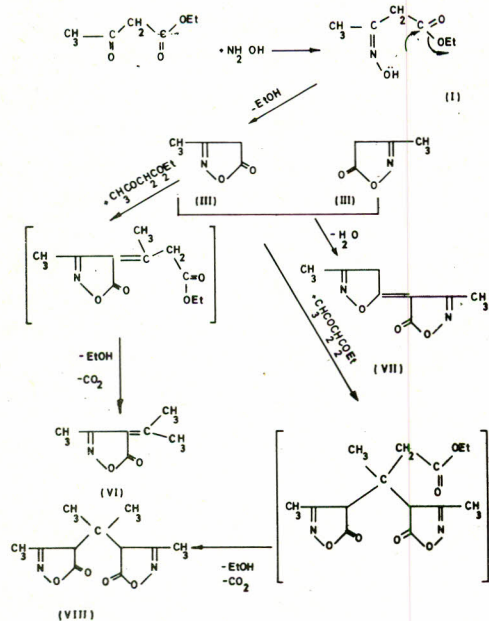
The addition of alkali (sodium hydroxide or morpholine) to the reaction mixture containing an equimolar

quantities of ethyl acetoacetate and hydroxylamine hydrochloride before the reaction is allowed to proceed in acidic medium, may determine the course of reaction to either (VI) (pH 10-11) or to (VIII) (pH 11-13). Strongly alkaline conditions (pH ≥ 13) and a low molar concentration (0.20 moles/litre) of ester and amine yields exclusively (VII) Table 1, 2 and 3.

Reactions carried out in all solvents used lead to the formation of (VI). Its maximum yield (67 %) is obtained in methanol at room temperature (20 ± 2°) Table 3.

The present studies provide conditions for the exclusive formation of (VI), (VII) and (VIII). Parameters have been determined which provide conditions for the independent formation of each one of them.

Reaction mechanism. The mechanism for the formation of these compounds has been suggested Reaction Scheme.



Scheme of reaction.

Ethyl acetoacetate and hydroxylamine are considered to form an ester oxime, which cyclises to yield 3-methylisoxazol-5-one (III). Depending upon the conditions prevailing in the reaction mixtures the methylene group of this isoxazolone may condense with the keto function in ethyl acetoacetate to yield an intermediate which undergoes hydrolysis and cleavage to yield 4-isopropylidene-3-methylisoxazol-5-one. It may be worthwhile to mention here that when the reaction of ethyl acetoacetate and hydroxylamine was carried out in acetone, both at room temperature and under reflux, the yield of compound (VI) was low. However, when the reaction was carried out at room temperature in methanol the yield of this compound improved considerably. If the acetone was participating in the reaction, the yield of (VI) would have improved. Thus, our studies support the earlier finding that acetone never participates in the formation of (VI) but no mechanism was proposed for it. Our proposed mechanism for the formation of this compound (VI) is by an intermediate without involving acetone. Thus, there is no role of acetone for the

formation of (VI). This may be attributed to the reduced electrophilic nature of the carbonyl carbon of acetone as compared with that of ethyl acetoacetate.

Among the other possibilities in the condensation of one molecule of ethyl acetoacetate simultaneously with two molecules of 3-methylisoxazol-5-one to yield as intermediate which decomposes to yield (VIII). It is also possible that one molecule of the isoxazolone will provide an active methylene group for condensation with the keto function of the other to yield an anhydride (VII).

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REFERENCES

1. B. Westenberger, Ber. Dtsch. Chem. Ges., **16**, 2996 (1883).
2. A. Hantzsch, Ber. Dtsch. Chem. Ges., **24**, 495 (1891).
3. R. Schiff, Ber. Dtsch. Chem. Ges., **28**, 2733 (1895).
4. G. Nussberger, Ber. Dtsch. Chem. Ges., **25** (Part II), 2142 (1892).
5. R. Schiff and M. Betti, Ber. Dtsch. Chem. Ges., **30**, 1337 (1897).
6. L. Knor and B. Reuter, Ber. Dtsch. Chem. Ges., **27**, 1174 (1894).
7. R. Uhlenhuth, Annalen., **296**, 33 (1897).
8. J.J. Donleavy and E.E. Gilbert, J.Am.Chem.Soc., **59**, 1072 (1937).
9. N.V. Khromov, Khim. Refrat. Zhur., **7**, 31 (1939).
10. A.E. Porai-Koshits and N.V. Khromov, J.Gen.Chem. USSR, **10**, 557 (1940).
11. N.V. Khromov and A.E. Porai-Koshits, J.Cen.Chem. USSR, **17**, 1816 (1947).
12. N.V. Khromov, J. Gen. Chem., **20**, 1858 (1950).
13. A.R. Katritzky, S. Oksne and A.J. Boulton, Tetrahedron **18**, 77((1962).
14. G. Lo Vechio, G. Lomonica and G. Gum. Bio-Chim. Appl., **10** (3), 131 (1963).
15. R. Jacquier, C. Petrus, F. Petrus and J. Verducci, Bull. Soc.Chim.Fr., **8**, 3003 (1967) (Fr).
16. T. Nishiwaki, J.Chem.Soc., (C), 363 (1969).
17. Schulz, Horst, Anal. Biochem., **37** (2), 457 (1970) (Eng).
18. N.N. Gosh and P.C. Chaudhry, J. Indian Chem. Soc., **49** (9), 915 (19750).