HANTZSCH SYNTHESIS IN AQUEOUS SOLUTION AT LOW pH RANGE. PART I

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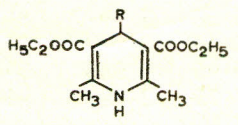
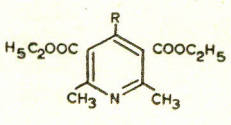
The synthesis of Hantzsch ester I_b in buffered solutions at a pH of 3-10 has been studied, It is observed that I_b is obtained in good yield (1-53%) at pH 3.25 to 5.0 in 1.0N acetic acid medium. This is in contrast with the observation of Haley and Maitland. The yellow impurity noted by them contains the pyridine derivative II_b along with some other compounds. β-Aminocrotonic ester (III) and α-ethylidene ethyl acetoacetate (IV) are the only intermediates during the formation of I_b. The 1,5- diketone reported by Knoevenagel and Klages does not give I_b with ammonia under the epxerimental conditions. Instead, a compound of structure VI is formed. The molecular ion at m/e 285 establishes the molecular formula of VI as $C_{14}H_{23}NO_5$. The NMR spectrum supports structure VII in some detail.

Haley and Maitland[1] observed that the variation of pH has striking effect on the yield of 1,4-dihydrocollidine-3,5-carboxylate (I_b). Using ($KH_2PO_4 \times NaOH$) buffers; they showed that the condensation takes place only within a pH range of 6–10, giving a maximum yield of 45% at pH 8.5. With 10% aqueous ammonium carbonate solution, they obtained a yield of 70% of nearly pure 1,4-dihydrocollidine-3,5-carboxylate I_b at pH 8.5. The difference of yields at the same pH, i.e. 8.5, shows that there are some other factors which affect the yield. We observed that I is formed at pH 3.5 to 5.5 in considerable quantities (1 to 53%) (Table 1). Haley and Maitland found no dihydropyridine (I_b) below pH 5.5.



I (a) R=H
(b) R=CH3



I (a) R=H
(b) R=CH3

It is observed that ethyl acetoacetate left overnight in 10% ammonium carbonate solution at room temperature gave β-aminocrotonic ester (III) in good yield. This shows that the β-aminocrotonic ester is an intermediate during the formation of I. α-Ethylidene ethyl acetoacetate (IV) was prepared in water at room temperature and when mixed with III, as such or in solvents like water and alcohol, readily gave the dihydropyridine I_b in good yield. Even when the two were mixed in citric acid solution (pH 2.2), they gave a few crystals of I_b.

The ammonium salts of strong acids, e.g. NH_4Cl and NH_4NO_3, in which availability of ammonia is comparatively low, give poor yield, even at higher pH values, whereas with the solution of ammonium salts of weak acids, reaction proceeds smoothly, at pH range 4–5 (Tables 1 and 2). It is inferred that the presence or liberation of ammonia is the key to the reaction. This also suggests that while the aldol and Michael condensations are base catalysed, a proton donor must also be available in overall reaction.

The yellow basic impurity reported by Haley and Maitland is found to be a mixture of pyridine derivative (II_b) of dihydro compound (I_b) and another basic yellow compound which gave a red coloration with picric acid.

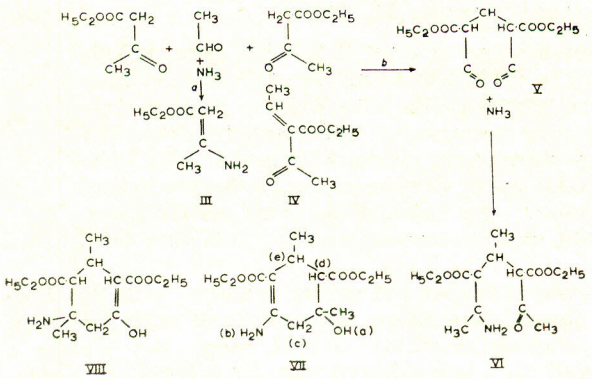
For determining the mode of formation of pyridine derivative (II_b) a few experiments have been carried out. Whereas dihydrolutidine dicarboxylate (I_a) was converted immediately into pyridine derivative on treatment with strong acids, dihydrocollidine dicarboxylate (I_b) was not changed into its pyridine derivative even with boiling hydrochloric acid.

On treatment with dilute hydrochloric acid and ammonium salts of strong acid no conversion takes place even in the case of dihydrolutidine dicarboxylate (I_b). If it were a case of disproportionation or air oxidation pyridine derivative would have been formed easily under these conditions. The acetic acid medium used in condensation reaction had no effect on these dihydro compounds. Similarly, oxidation with formaldehyde and acetaldehyde did not take place. When an aldehyde and acetoacetic ester are condensed in the presence of a secondary or tertiary base, no pyridine derivative is formed. It has been observed[2] that hydrogen transfer from Hantzsch ester to chloranil is virtually complete in 15 min.

The formation of pyridine derivative seems to be due to the oxidation of dihydro compound

by some ketonic compounds[3] formed during the condensation.

The following mechanism is proposed for these reactions:



The first stage of route *a*, the formation of α-ethylidene acetoacetate, and β-aminocrotonic ester was first confirmed by Beyer.[4] Our observation also supports this mechanism; no 1,5-diketone (V) could be isolated in our experiments. The 1,5-diketone (V) prepared separately and treated with an aqueous solution of an ammonium salt or with anhydrous ammonia in organic solvents does not give any dihydro compound. However, the reaction of V with anhydrous ammonia in alcohol yields a compound of structure VI.

The molecular ion at m/e 285 establishes the molecular formula $C_{14}H_{3}NO_5$. The NMR spectrum supports in some detail structure VII or VIII. One proton singlet at $\tau=6.57$ and a broad two proton singlet at $\tau=3.86$ can be removed from the spectrum on shaking the deuterochloroform solution of the compound with deuterium oxide; these signals are assigned to H(a) and H(b), respectively. The protons of the isolated CH_2 group H(c) resonate as an AB system ($\tau=7.50$, $\tau=7.77$) with $J=$ 16 c/s. H(d) resonates as a doublet ($J=7$ c/s) centred at $\tau=7.75$, while H(e) is evident as a pair of quarters centred at $\tau=6.90$. The signals associated with the methylenes of the ethoxyl groups occur as a four proton multiplet centred at $\tau=5.68$. The integration trace establishes the presence of four C-methyl signals in the $\tau=8.4$–8.8 region.

Compound VI was first isolated by Rabe and Billmann.[5] Knoevanagel and Klages [6] reported that I_b was formed when VI was treated with ammonia. Rabe and Billmann[5] demonstrted that the observation made by Knoevanagel and Klages,[6] was not correct. Later on, Rabe and Elze[7] stated that treatment of diketone with alcoholic ammonia resulted in the formation of dihydropyridine. But they could not isolate the pure diketone V. However until recently, V has been suggested as one of the intermediates[6] for the formation of dihydropyridine.

TABLE 1.—YIELD OF DIETHYL 1,4-DIHYDRO-COLLIDINE-3,5-DICARBOXYLATE AT DIFFERENT pH VALUES AT ROOM TEMPERATURE.

Time (days)	pH initial	pH final	Yield g	Yield %
7 days	3.4	3.25	0.0394	0.75
acetic	4.0	3.75	0.2974	5.67
acid	4.1	4.00	0.532	10.13
	4.2	4.10	0.5779	10.07
	4.3	4.15	0.710	13.52
$K_a=1.8\times10^{-5}$	4.4	4.30	0.779	14.83
	4.5	4.30	0.7975	15.19
	4.6	4.40	0.965	18.4
	4.7	4.50	1.038	19.7
	4.8	4.65	1.125	21.43
	3.4	3.25	0.0394	0.75
	3.95	3.75	0.2545	4.85
	4.90	4.75	0.926	17.62
4 days	5.00	4.75	2.8015	53.36
	6.00	5.53	3.0017	57.17
	7.00	5.50	3.0428	56.25
	8.00	5.65	2.953	56.25
	9.00	7.75	3.3975	64.33
14 days	4.00	3.65	–	—
succinic	5.00	4.10	4.3678	7.00
acid	6.00	4.40	1.3092	19.80
$K_1=9.2\times10^{-5}$	7.00	4.40	1.219	23.22
$K_2=5.3\times10^{-6}$	8.15	4.40	1.300	24.76
	9.00	4.75	1.6811	32.02
	10.00	4.65	2.2372	42.6

Experimental

Experiments recorded in Tables 1 and 2 were performed in stoppered flasks at room temperature (20-37°). Ethyl acetoacetate and acetaldehyde were pure samples and all other reagents were of "Analar" grade. The m.ps quoted are uncorrected and adjustment of pH values was carried out with Cambridge Bench pH meter.

TABLE 2.—YIELD OF DIETHYL 1,4-DIHYDRLCOLLIDINE-3, 5-DICARBOXYYLATE AT DIFFERENT pH VALUES AT ROOM TEMPERATURE.

Acid or salt	Time	pH initial	pH final	Yield g	Yield %
		3.10	—	—	—
Oxalic acid		4.00	3.45	0.109	2.08
$Ka_1 = \times 10^{-2}$		5.00	3.65	0.3228	6.15
$Ka_2 = 1.3 \times 10^{-4}$		6.00	3.70	0.393	7.46
	14 days	7.55	3.70	0.3945	7.51
		8.00	3.75	0.4022	7.66
		9.00	3.90	1.102	20.99
		10.00	8.30	1.512	28.8
		5.40	2.00	.130	2.47
		6.85	4.70	.134	2.55
		7.00	6.25	.148	2.82
		8.00	7.25	.895	17.04
		9.00	8.20	1.9195	36.56
		10.00	9.70	.0752	1.43
NH_4Cl*					
		5.25, 6.10, 7.0, 8.0	Oil on this pH value		
$(NH_4)_2SO_4$ *		9.0	8.35	1.052	20.04
		9.3	9.05	1.277	24.3

*In these cases the yield depends mostly on the concentration of the salts. There is a possibility that no condensation takes place even at pH 9 or 10 while at lower pH with low concentration condensation does take place even at pH 5.0 with reasonable amount (6%) of compound.

Solution.—The concentration of acids in water were adjusted after a number of trials. The minimum possible concentration (0.1M of oxalic acid and succinic acid) was preferred for the isolation of pure dihydro compound. A higher concentration of acetic acid (1.0N) was used to isolate the yellow substance. The concentration (10%) of the salts was the same as taken by Haley and Maitland for a comparative study.

The acid solution (200 ml) was taken in flasks and the pH was adjusted by the addition of ammonium hydroxide. Ethyl acetoacetate (5.2 ml, 0.04 mole) and acetaldehyde (1.2 ml, 0.02 mole) were added in each flask. The reaction mixture was filtered and the dihydro compound I_b purified by washing with dilute hydrochloric acid or petroleum ether. The dihydro compound (m.p. 92-100°C) isolated at pH 5–6 was highly contaminated with the yellow substance and pyridine derivative of the dihydro compound. It was dissolved in strong hydrochloric acid and the solution was diluted with water until turbidity appeared. Compound I_b crystallised out (m.p. 130-131°C).

The filtrate was neutralised with alkali and extracted with ether. The extract was dried (Na_2SO_4) and a solution of picric acid in ether was added to it. Within 15 min II_b picrate (m.p. 152-155°) crystallised out. When the derivative of II_b was small, it took 24 hr for the picrate to crystallise out and a dull red coloration appeared along with crystals of picrate of II_b. This picrate was again decomposed with alkali and the pyridine derivative was extracted with ether. The ethereal extract was dried (Na_2SO_4) and concentrated *in vacuo* when an oily compound of high boiling point was obtained. This oil and its picrate were analysed. Oil, Found: C, 63.38; H, 6.99; N, 5.6. $C_{14}H_{19}O_4N$ requires: C, 63.6; H, 7.1; N, 5.3. Picrate, Found: C, 48.52; 4.62; N, 11.02; $C_{14}H_{19}O_4N$. $C_6H_3O_7N_3$ requires: C, 48.58; H, 4.45; N, 11.33%.

An authentic sample of II_b was prepared by oxidizing dihydro compound and its picrate (m.p. 152-155) was then prepared. Mixed m.p. determination showed no depression. The yellow impurity and II_b can also be isolated with petroleum ether. The yellow substance and II_b were soluble in petroleum ether whereas I_b was insoluble.

Acetoacetic ester (5.2 ml, 0.04 mole), acetaldehyde (1.2 ml, 0.02 mole) and a drop of secondary or tertiary base such as pyridine, piperidine or diethylamine were added to water (200 ml). A white turbidity appeared. The reaction mixture was left overnight when an oily layer settled down. On adding ammonium salts, no yellow coloration appeared and the yield of I_b was increased. In case of formaldehyde, II_b crystallised out when the solutions of the ammonium salts were taken but no pyridine derivative was observed when ammonium salts were added after the addition of secondary or tertiary base.

β-Aminocrotonic Ester (III).—Ethyl acetoacetate (10.4 ml, 0.08 mole) was added to 10% ammonium carbonate solution (100 ml) and the mixture left overnight at room temperature. A white turbidity appeared and an oily layer separated out. The oily layer was extracted with ether and, after the removal of ether, it distilled at 68–70°/2.5 mm. (Found C, 56.0; H, 8.6; N, 10.5. $C_6H_{11}O_2N$: requires: C, 55.8; H, 8.58; N, 10.85%).

α-Ethylidine Acetoacetate (IV).—Ethyl acetoacetate (10.4 ml, 0.08 mole) and acetaldehyde (2.4 ml, 0.04 mole) were added to water (200 ml) along with a drop of piperidine. The reaction mixture left overnight at room temperature, and then extracted with ether. After the removal of ether, the liquid distilled at 50-52°/0.1mm. (Found C, 61.40; H, 7.60. $C_8H_{12}O_3$ requires: C, 61.52; H, 7.75%).

4-*Methyl-2-aminohepten-*(2)-*on*(6)-*diethyl ester-*(3,5) (VI).—The 1,5-diketone was prepared according to the method of Horning, Denekas and Field.[9] It melted at 77°, lit.[9] 75-77.5%. (Found: C, 58.83; H, 7.2. $C_{14}H_{22}O_6$ requires: C, 58.7; H, 7.75%). The diketone (10 g) was dissolved in absolute ethanol (20 ml), and anhydrous ammonia was passed at 0°C till the solution was saturated. The reaction mixture was left overnight in the refrigerator. 4-Methyl-2-aminohepten-(2)-on(6) diethyl ester crystallised out (5.0 g), m.p. 138° (lit. 140°). (Found: C, 58.8; H, 8.21; N, 5.01. $C_{14}H_{23}NO_5$ requires: C, 58.93; H, 8.13; N, 4.91%.)

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One of us (A.E.) prepared VI in University Chemical Laboratory, Cambridge, while on a short visit.

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