

CONDENSATION OF ALDEHYDES WITH MALONIC ACID

Part XII. The Influence of Groups and of other Factors

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THE reduced yields of the hydroxy-cinnamic acids obtained from the condensations of malonic acid with hydroxy-benzaldehydes have been generally recognised as due to the steric hindrance caused by the hydroxyl group present on the nucleus. This is most evident in the case of salicylaldehyde where the hydroxy group is *ortho* to the aldehyde group. That this inhibitive effect is appreciably, and sometimes largely, modified, when the hydroxy group is replaced by the methoxy group has also been pointed out in an earlier paper.¹ In the same paper was also pointed out the increase in the inhibitive influence in the case of 2:4-resorcyaldehyde, wherein the nucleus contained two hydroxy groups, one of which was *ortho* to the aldehyde. The highest yield obtained here was only 46%, in contrast with 64% obtained in the case of the mono-hydroxy aldehyde, salicylaldehyde.

These observations are further corroborated in the present paper wherein the condensations of protocatechuicaldehyde, vanillin and veratraldehyde under comparable conditions have been investigated. The three may be looked upon as belonging to a series, with two hydroxy groups in protocatechuicaldehyde, one hydroxy and one methoxy group in vanillin and two methoxy groups in veratraldehyde. It is found that the condensations are progressively easier, quicker and more successful in the yields of the corresponding cinnamic acid derivatives.

The protocatechuicaldehyde gave 44% yield of caffeic acid, indicating that the steric hindrance is as powerful as it was in the isomeric 2:4-resorcyaldehyde, though in the present case none of the two hydroxy groups stands in the *ortho* position to the aldehyde group.

Vanillin, on the other hand, gave an appreciably higher yield of 51.5%, in a shorter time, *i.e.*, in 3.5 hours, of ferulic acid. And Veratraldehyde gave,

on two hours' heating, 57.6% and on a further two hours' heating, at a slightly higher temperature, 62.5% yields of dimethoxy-cinnamic acid.

The condensations in the above cases were brought about in the manner usual in the series, *viz.*, with the help of a trace of pyridine. Dutt on using the carbethoxy-derivatives of the first and the second had obtained, with the pyridine-piperidine mixture, only 7 and 12% yields respectively,² though, some years later, he obtained comparable yields by using quinoline in molecular proportions.³

The real progress in the case of these condensations is clearly demonstrated in the results obtained when the aldehydes were allowed to react alone with malonic acid without the presence of even a trace of a base or of any condensing agent. The three aldehydes in this case gave the following yields of the same acids, 16.6, 61.8 and 86.5 per cent. respectively and in a progressively shorter time (Table I). That the yields in the case of the last

TABLE I

	Molecular proportions			Temp.	Time	Yield %
	Alde.	Acid	Base			
Protocatechuic-aldehyde ..	1	1	0.15 pyridine	water-bath	5-6 hrs.	44.4
	10
	4 ..	44.4
	1	1	0.0 no base	..	5 ..	16.6
Vanillin ..	1	1	0.15 pyridine	70°	3.5 ..	51.5
	1	1	0.0 ..	80°	61.8
Veratraldehyde..	1	1	0.15 ..	water-bath	2 ..	57.6
	+ 110°	2 ..	
	1	1	0.0 ..	water-bath	3.6 ..	86.5

two should have been higher in the absence than in the presence of a condensing agent is very striking.

Other condensing agents were tried in the case of protocatechuicaldehyde, in order to increase the yield if possible, *viz.*, piperidine, pyridine-piperidine mixture as used by Robinson and Shinoda⁴, concentrated sulphuric acid, dry hydrogen chloride in the presence of absolute alcohol, etc., but the results

were disappointing. Hayduck has applied Stuart's method of using glacial acetic acid in place of a base⁵ to protocatechualdehyde, and this method gave the yield of about 77%.

Recently Fritz Vorsatz⁶ has reported an improvement in the synthesis of hydroxy-cinnamic acids. He employs the same materials in almost the same proportions as Robinson and Shinoda, *i.e.*, the aldehyde malonic acid, pyridine and piperidine in 1 : 2 : 6 : 0.1–0.2 mol. proportions, but instead of the high temperature of the latter, he keeps the mixture at room temperature, for three weeks. Knoevenagel had done this in several successful condensations and this principle of so to say substituting time in place of temperature has enabled Fritz Vorsatz to obtain almost record yields, *viz.*, 87% caffeic acid from photocatechualdehyde, 73% ferulic acid from vanilline and 83% of piperonylacrylic acid from piperonal.

Although 'the room temperature' is an exceedingly elastic phrase, and although the room temperature in Agra might hardly be comparable with the temperature of Vorsatz's rooms, experiments were tried on the same model here in Agra in the cold weather, and entirely confirmed his findings (Table II). Protocatechualdehyde gave as much as 83%, and vanillin 71.4% yield. The higher yield of the former seems to be anomalous and suggests as if the inhibitive effect of the hydroxy group underwent another modification at low temperatures. It has also to be observed that when

TABLE II

	Molecular proportions			Temp. approximately	Time	Yield %
	Alde.	Acid	Base			
Protocatechualdehyde ..	1	2	6 pyridine + piperidine trace	10°–25°	3 weeks	83.0
	„	„	„ „ + „	25°–45°	3 months	46.1
	1	2	0.21 „ + „	5°–20°	3 weeks	76.9
	1	2	0.21 pyridine	„	„	69.2
Vanillin ..	1	2	6 pyridine + piperidine trace	10°–25°	3 weeks	71.4
	1	2	0.39 „ + „	25°–45°	3 months	62.0
	1	2	0.39 „ + „	25°–20°	3 weeks	69.7
	1	2	0.39 pyridine	„	„	62.
Veratraldehyde ..	1	2	0.4 pyridine	„	„	81.7

the protocatechuicaldehyde mixture was kept for three months in the summer instead of three weeks in the winter, the yield was not further increased, but was, on the contrary, reduced to 46%.

Would the method of Vorsatz answer equally well when the bases were in traces only, or when there was only one base pyridine in a trace? This question has been faced and the answer is in the affirmative, the yields being almost the same, namely, about 77, 70 and 82% respectively from the three aldehydes. Further experimentation may assist in finding out conditions of better or theoretical yields, but as for practical purposes few would employ synthetic methods requiring three weeks or so, it is considered sufficiently satisfactory to note the efficiency of traces even in this method.

It may be observed that the complete suppression of the steric hindrance exercised by the two adjacent hydroxy-groups is demonstrated in the condensations of piperonal, wherein the two hydroxy groups are replaced by a methylene-dioxy-group and which has given almost quantitative yields.⁷

The nitro-group offers a kind of contrast to the hydroxy-, as the three nitro-benzaldehydes undergo the condensation easily and give very good yields of the corresponding nitro-cinnamic acids. These have been very well studied by a number of workers employing different methods. The pyridine-trace method has been recently applied by Rangaswami, Rao and Seshadri⁸ to prepare *o*-nitro- and *m*-nitro-cinnamic acids. As they have not mentioned their yields, and as they did not study *p*-nitro-benzaldehyde, these are given below. It may be noted that here in each of the three cases the condensations proceed even when no base is present and the yields are, in the same period of time, over 50%.

Experimental

(With T. S. Sodhi)

The Condensation of Protocatechuicaldehyde and the Synthesis of Caffeic Acid.—2.7 g. Aldehyde, 2 g. malonic acid and 0.25 c.c. pyridine (1 : 1 : 0.15 mol.) were heated on a water-bath for 5-6 hours. The mass fused in 1.5 hours, then bubbling started, and then it gradually set to a solid. The product contained the unused aldehyde which was removed by refluxing with alcohol and animal charcoal. The caffeic acid so obtained weighed 1.6 g. (44.4%) and was of a light brown colour melting at 200°.

Longer heating gave a tarry mess, but the same yield was obtainable on 4 hours' heating. The yield diminished to 38.8% when the time of heating was reduced to 3 hours. When heated without a base 1.3 g. aldehyde gave

only 0.3 g. or 16.6% yield, which, however, gave a better melting-point (209°). When 0.15 mol. of piperidine was substituted, the yield was 16.6% on 5 hours' heating.

When a molecular quantity of pyridine was taken, or the still greater proportions according to Robinson and Shinoda (*loc. cit.*), a black resinous mass was obtained which yielded no caffeic acid.

Hayduck's Method.—3 g. Aldehyde, 3 g. malonic acid and 2 g. glacial acetic acid were heated on the water-bath for ten hours. The whole mass was a homogeneous liquid in half an hour and became brown in colour. Bubbles then came off. At the end the cooled mass was treated with water when an ash-coloured precipitate came down. It was filtered, and purified: it weighed 3 g. = 76.9% yield.

Vorsatz's Method.—2.5 g. Aldehyde, 3.85 g. malonic acid, 8.5 c.c. pyridine and 0.1 c.c. piperidine were kept in a loosely corked flask for three weeks at room temperature (ranging between 10° and 25° C. approximately). Water was then added and ammonium carbonate solution. The filtrate was acidified and extracted with ether. The ethereal extract when worked up gave 2.7 g. or 83% of caffeic acid.

Another flask containing the same mixture was left for three summer months, when the room temperature might have fluctuated between 25° and 45° C. The yield when worked up came only to 46%. But when instead of 6 mol. proportion of pyridine only 0.21 was taken, with or without additional trace of piperidine, the yields were quite good (*vide* Table II).

Condensation of Vanillin: Synthesis of Ferulic Acid.—3.1 g. Vanillin, 2.1 g. malonic acid, and 0.3 c.c. pyridine (1 : 1 : 0.15 mol.) heated at 70° for 3.5 hours gave 2 g. of ferulic acid, melting at 169°. The yield was poorer if higher temperatures were employed.

0.75 g. Vanillin, heated alone with 0.5 g. of malonic acid at 80° for 3.5 hours, gave 0.6 g. or 61.8%.

The yields obtained by Vorsatz method are given in the table.

Condensation of Veratraldehyde.—Veratraldehyde, obtained, by the methylation of vanillin, 1.6 g., malonic acid 1 g. and pyridine 0.12 c.c., on being heated on the water-bath for 2 hours, gave on being worked up in usual way, 1.2 g. (= 57.6% yield) of dimethoxycinnamic acid, m.p. 180°. When the heating was supplemented with another 2 hours' heating at 110°, the yield improved to 62.5%.

The same heated without pyridine, yielded 1.8 g. or 86.5%. Almost the same yield was obtained when the three, in 1 : 2 : 0.4 mol. proportions,

were kept for three weeks at room temperatures according to Vorsatz' method modified.

(With Dilbahar Singh Mittal)

Condensations of o-, m- and p-Nitrobenzaldehydes.—The procedure was exactly the same in the three cases: 1.5 g. of the aldehyde, 1.2 g. malonic acid and a trace of pyridine, (1:1:0.15 mol.) were heated on the water-bath for four hours. The three nitrocinnamic acids, taken out as usual, were all *trans*-nitrocinnamic acids and melted at 242.7° and 200° and 286° respectively. Piperidine and quinoline traces were also similarly employed and gave slightly lower yields. The reaction in each case went on also in the absence of any base, by heating the two together, and as judged from the yields in the same period of time, was half complete only.

TABLE III

Aldehyde	Molecular Proportions			Yield %
	Alde.	Acid	Base	
<i>o</i> -Nitrobenzaldehyde ..	1	1	0.15 pyridine	90.7
 piperidine	88.1
 quinoline	82.9
	1	1	0.0 no base	51.8
<i>m</i> -Nitrobenzaldehyde ..	1	1	0.15 pyridine	88.0
 piperidine	85.5
 quinoline	80.4
	1	1	0.0 no base	52.8
<i>p</i> -Nitrobenzaldehyde ..	1	1	0.15 pyridine	87.6
 piperidine	85.0
 quinoline	75.1
	1	1	0.0 no base	51.9

Summary

Condensations of protocatechuicaldehyde, vanillin and veratraldehyde with malonic acid in the presence of various proportions of bases, and in the absence of any base, show that the hydroxy-group generally diminishes the yield, which rises when the group is methylated. Influences of different proportions of the base, and of different temperatures and periods of time at

which the reactions are allowed to proceed are recorded. The trace of the base is generally as efficient as ever. The nitro-group on the other hand, when present on the nucleus, is not found to exert any restraining influence on the yields obtained, and allows very high yields of the nitro-cinnamic acids.

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