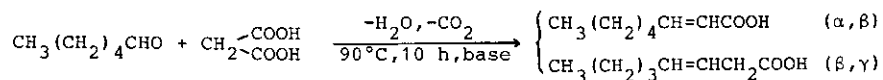


INFLUENCE OF HETEROAROMATIC AMINES TO KNOEVENAGEL CONDENSATION

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Abstract—— In the Knoevenagel condensation of hexanal and malonic acid, the ratio of α,β - and β,γ -unsaturated acids was remarkably affected by the nature of tertiary amines used as a catalyst. That is, the condensation in pyridine or isoquinoline gave 2-octenoic acid selectively, whereas the condensation in 2-methylpyridine, 2,6-dimethylpyridine, or quinoline gave 3-octenoic acid as a main product.

The Knoevenagel condensation of aliphatic aldehydes having a straight carbon chain with malonic acid in the presence of an appropriate organic base in accompanied with decarboxylation is widely used in the synthesis of unsaturated fatty acids.¹ However, the condensation does not always give an α,β -unsaturated acid which is simply anticipated as the main product of the reaction. For example, an aldehyde reacts with malonic acid to give an α,β -unsaturated acid in one mole equivalent of triethanolamine, while the reaction of the same substrate in one mole equivalent of pyridine gives the corresponding β,γ -unsaturated acid.² Since no description was given to explain the mode of the condensation mentioned above, we re-investigated the condensation of aldehydes with malonic acid using hexanal as a substrate, and obtained clear results on the relationships between the structure of the tertiary amines and the location of the carbon-carbon double bond in the resulting octenoic acids.



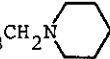
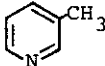

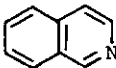
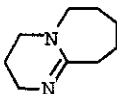
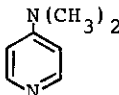
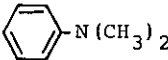
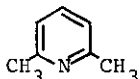
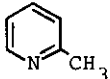
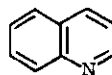


Scheme 1

In order to standardize the reaction conditions, the experiments were designed as follows: a mixture of equimolecular amount of hexanal, malonic acid, and an organic base was stirred under nitrogen atmosphere for 10 h at 90°C. At the early stage of heating, carbon dioxide evolved vigorously. Then the resulting solution was poured

into ice-water containing 20 % sulfuric acid. The octenoic acids were extracted with methylene chloride, and the extract was treated with ethereal diazomethane to convert the acids into their methyl esters. The mixture of the esters was analyzed by use of gas chromatography. The total yields and the ratio of 2-octenoate and 3-octenoate were listed in Table I, together with the pKa values of the bases employed as the catalyst.³

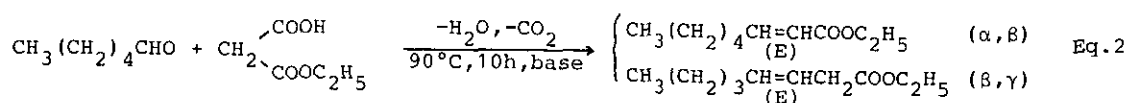
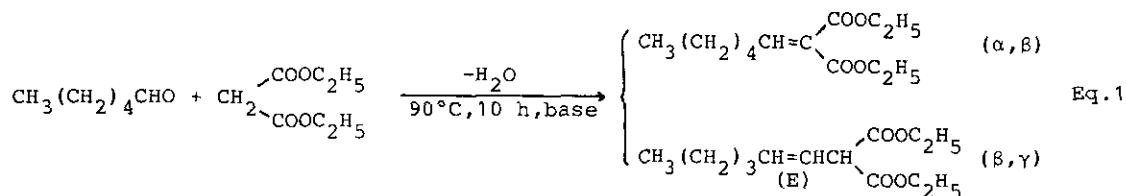
Table 1

Group A					Group B				
tert. amine	pKa	yield (%)	ratio α, β β, γ		tert. amine	pKa	yield (%)	ratio α, β β, γ	
$N(CH_2CH_2OH)_3$	7.77	48	2	98		5.2	64	91	9
$N(CH_2CH_3)_3$	10.87	76	2	98		6.08	64	88	12
	10.40	62	2	98		5.52	75	90	10
	8.7	47	10	90		5.4	48	64	36
	11.5	56	6	94		9.70	48	64	36
	5.15	31	1	99					
	6.8	56	4	96					
	6.2	62	17	83					
	4.9	65	33	67					

As shown in Table I, the amines used in the experiments are recognized to be classified into two groups. The amines in group A are those controlled the condensation selectively to give 3-octenoic acid, and group B consists of the amines which catalyzed the reaction to give 2-octenoic acid mainly. The characteristics of the amines in group B are that they have a basic center with no steric hindrance, whereas the basic center of the amines in group A, in comparison with those in group B, seems to suffer from steric effect to a certain extent. In view of the data listed in Table I, the steric circumstances of the basic center in these amines have an important role rather than the basicity. For example, there is not much difference in pKa values


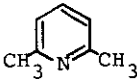
among pyridine, 2-methylpyridine, and 2,6-dimethylpyridine, but the ratio of the products are strikingly different. Another example is a set of quinoline and isoquinoline. The catalytic action of quinoline giving 3-octenoic acid mainly, may result from the presence of a hydrogen atom at the peri-position, because isoquinoline leads the reaction to form 2-octenoic acid. On the other hand, 1,8-diazabicyclo[5.4.0]undec-7-ene has the highest pKa value among the tested bases, and the basicity of dimethylaniline is nearly equal to that of pyridine, but the both amines acted as the catalyst to give 3-octenoic acid selectively. Judging from the product ratio, the catalytic function of triethanolamine and that of triethylamine were equivalent. Therefore, it is clear that the hydroxyl groups in the former compound has no significant role in the deconjugation.

Further attempts were made to obtain more detailed information about the deconjugation during the condensation. Firstly, hexanal was allowed to react with diethyl malonate in triethylamine, pyridine, or 2,6-dimethylpyridine. As shown in Table II, in all these cases, the reaction proceeded to give the α,β -unsaturated esters, diethyl hexylidenemalonate, mainly. In contrast to the above, the reaction of hexanal with the half ester of malonic acid was remarkably affected by the amines used as the catalyst. Namely, the use of pyridine afforded ethyl 2-octenoate mainly, while the use of triethylamine gave ethyl 3-octenoate selectively. Alkaline hydrolysis of diethyl hexylidenemalonate obtained above under mild conditions gave the free dicarboxylic acid (d in Scheme 3), although it contains a trace amount of 1-hexenylmalonic acid. When the dicarboxylic acid (d) was treated with pyridine, the ratio of 2-octenoic and 3-octenoic acids was 86:14. On the contrary, the treatment of the same dicarboxylic acid with triethanolamine under identical conditions afforded 3-octenoic acid predominantly.

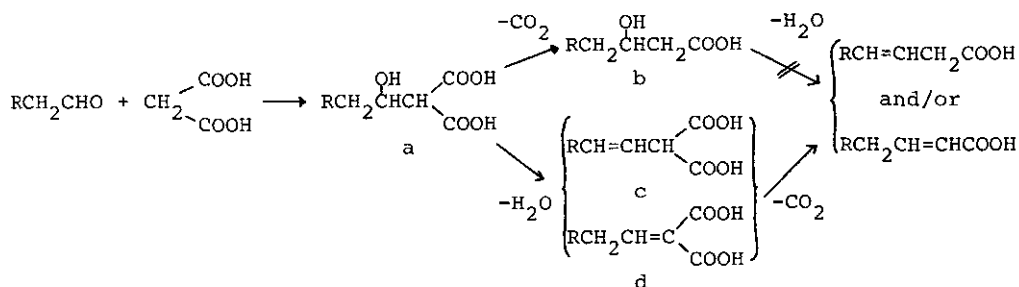


Scheme 2

Table 2

base	Eq. 1		Eq. 2	
	α, β	β, γ	α, β	β, γ
$N(CH_2CH_3)_3$	85	15	3	97
	76	24	94	6
	76	24	—	—

Finally, no isomerization was observed, when 2-octenoic and 3-octenoic acids were respectively heated in pyridine or triethylamine at 90-100°C for 10 h. When 3-hydroxyoctanoic acid (b in Scheme 3) was heated with pyridine or triethylamine, the reaction resulted in the complete recovery of the starting acid. The isolation of the possible intermediates (a,b,c, and d in Scheme 3) was unsuccessful, but on the basis of our observations, the deconjugation was concluded to be induced by the decarboxylation. The reaction pathway was tentatively shown below.



Scheme 3

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1. G. Jones, "Organic Reactions", ed. by A. C. Cope, John Wiley & Sons Inc., New York, Vol. 15, pp. 204-599 (1967).
2. S. E. Boxer and R. P. Linsted, *J. Chem. Soc.*, 1933, 740.
3. The methyl octenoates obtained herein have trans configuration regardless of the position of the double bond.

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