

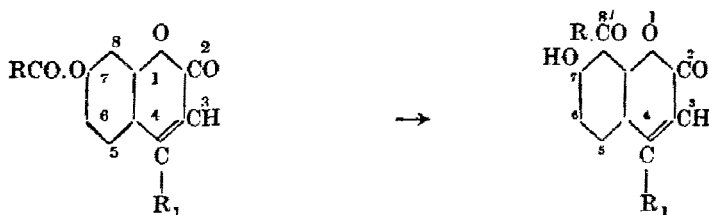
# STUDIES IN FRIES MIGRATION. PART I. THE FRIES MIGRATION OF ESTERS OF 7-HYDROXY-4-METHYLCOUMARIN

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Little systematic work has been done on the Fries migration of the hydroxy-esters of the coumarins. The work described in this paper was therefore undertaken and 7-acetoxy- and 7-benzoyloxy-4-methylcoumarins have been subjected to the Fries migration with a view to investigating the effect of various factors on the migration. The results show that (i) three mols. of  $\text{AlCl}_3$  are necessary to effect the migration, (ii) nitrobenzene as a solvent facilitates the reaction with better yields, (iii) the change in the conditions of the migration fails to effect the direction of the migrating group, which predominantly occupies the '8' position of the coumarin nucleus, and (iv) the benzoyl group requires a higher temperature for migration.

Since its discovery in 1909, the Fries migration has been extensively employed with the esters of mono- and poly-hydroxy phenols (i) as a method for the preparation of phenolic ketones and (ii) with a view to investigating its mechanism (Blatt, *Chem. Rev.*, 1940, 27, 418). Little systematic work appears to have been done on the Fries isomerisation of hydroxycoumarin esters, though during the last few years, it has been extended to this series by several workers.

Limaye and his co-workers (*Ber.*, 1932, 65, 375; 1934, 67, 12; *Rasayanam*, 1936, 20: 1937, 93; 1938, 141; 1939, 187) have carried out the Fries migration of various esters of 7-hydroxycoumarin derivatives and in all cases, obtained predominantly the 8-acyl-coumarin derivatives, in some few cases accompanied with traces of the 6-acyl isomer.



In 5-hydroxycoumarin series, different esters on being subjected to the Fries reaction gave 5-hydroxy-6-acyl-coumarin derivatives (Sethna, Shah and Shah, *J. Chem. Soc.*, 1938, 228; Shah and Shah, *ibid.*, 1938, 1424; Deliwala and Shah, *ibid.*, 1939, 1250). Desai and Mavani (*Proc. Indian Acad. Sci.*, 1942, 15A, 1, 10) were unsuccessful in effecting the Fries migration of 6-acetoxy-4-methylcoumarin. Shah and Shah (*J. Indian Chem. Soc.*, 1942, 19, 481) could successfully effect the Fries migration of ethyl 7-acetoxy-4-methylcoumarin-3-acetate and obtained 7-hydroxy-8-acetyl-4-methylcoumarin-3-acetic acid. All the above transformations were carried out mainly for the preparation of the specific compounds.

It is well known that in Fries migration, the position, relative to the hydroxyl group, which will be occupied by the migrating acyl group depends upon (i) the temperature at which the reaction is carried out, (ii) the nature of the acyl group and (iii) the phenol. The varying amounts of the migrating agent as well as the use of the solvent also influence the course of the reaction. No systematic work appears to have been done so far to

investigate the influence of these factors on the Fries migration of esters of hydroxy-coumarins.

The present investigation was therefore undertaken to study the influence of the above factors on the course of the Fries reaction; acetyl and benzoyl derivatives of 7-hydroxy-4-methylcoumarin were selected for the purpose.

*Effect of Aluminium Chloride.*—The amount of the migrating agent is known to have a considerable effect on the migration (Ralston *et al.*, *J. Org. Chem.*, 1940, 5, 645). Our observations also support this. With less than three moles of aluminium chloride, the product was exclusively 7-hydroxy-4-methylcoumarin in case of the acetoxy derivative, while some unreacted ester was recovered in case of the benzoyloxy derivative, along with the debenzoylated product and no migration product could be isolated. This clearly shows that at least three molecules of aluminium chloride are required for the acyl group to migrate; while with less amount of the same, only the cleavage product is formed.

It is well known that aluminium chloride forms addition complexes with compounds containing oxygen (Thomas, "Aluminium Chloride in Organic Chemistry", pp. 48-54). Since in coumarin there are O and CO in '1' and '2' positions, which can form complexes, it is probable that 2 moles are utilised in the complex formation. If such a complex formation takes place, no reaction will be effected till aluminium chloride is equal to or less than two moles and will be complete only if the amount is three moles.

*Effect of Temperature.*—Numerous workers (Eikmann, *Chem. Weekblad*, 1904, 1, 453; 1905, 2, 59, 79; Rosenmund and Schnurr, *Annalen*, 1928, 460, 56) have observed the influence of temperature on the Fries reaction; low temperature favouring the *para* migration, while the higher temperature, leading to the *ortho* migration. In this investigation, the *para* migration is not possible, but there are two *ortho* positions favourable and the different conditions may direct the groups differently. We find that no migration takes place at room temperature and the migration increases with the rise in temperature. A temperature as high as 130-140° is necessary for complete migration, the acyl group predominantly occupying the 8-position of the coumarin nucleus.

It is clear that the change in temperature has no influence on the position taken up by the acyl group. Further, the increase of temperature has little effect when the amount of aluminium chloride is less than 3 moles. It was also observed that actually the reaction is over within 15 to 20 minutes, because the evolution of HCl gas was vigorous during that period after which it slowed down.

*Influence of Solvent.*—Literature shows conflicting views about the role played by a solvent in determining the course of the reaction. Some think that the solvent may effect the ease and extent of the reaction but has little effect in directing the migration in a particular position (Baltzly and Bass, *J. Amer. Chem. Soc.*, 1933, 55, 4292; Fieser and Bradsher, *ibid.*, 1936, 58, 1738, 2337); others are of the opinion that solvent has profound influence (Ralston *et al.*, *loc. cit.*). We found that nitrobenzene as solvent had made the reaction smooth and rapid with an improvement in the yield of the product. However, it had little effect when aluminium chloride was less than 3 moles, nor did it exert any influence in directing the migrating group.

*Nature of the Acyl group.*—That the rate of migration varied with different acyl groups has long been observed (Rosenmund and Schnurr, *loc. cit.*; Baltzly and Bass,

*loc. cit.*). We find that the acetyl group is easily split off the oxygen atom while the benzoyl is rather firmly held. Further, the benzoyl group requires a higher temperature for migration than the acetyl group.

In all cases, it was observed that the main product of the Fries reaction was 7-hydroxy-4-methyl-8-acyl-coumarin, a trace of 6-acyl isomer being obtained in the case of the acetyl derivative and that only in few cases. The benzoyl derivative gave in no case the 6-benzoyl derivative even in a trace. The change of conditions failed to change the course of the reaction, proving that the '8' position is more reactive than '6.' This reactivity can be explained on the theory of 'Fixation of Double Bonds' first advanced by Mills and Nixon (*J. Chem. Soc.*, 1930, 2510). The migrating group attaches to that C atom which is bound by a double bond with the C atom bearing the hydroxyl group.

## EXPERIMENTAL

7-Acetoxy- and 7-benzoyloxy-4-methylcoumarins were prepared according to Pechmann and Duisberg from  $\beta$ -methylumbelliferone (*Ber.*, 1883, 16, 2124).

*General Method of carrying out the Fries Migration. (i) In Nitrobenzene as a Solvent.*—The ester was dissolved in the dry solvent; a solution of anhydrous aluminium chloride in the same solvent was added. The mixture protected from moisture (CaCl<sub>2</sub>-guard tube) was left at room temperature or heated to the required temperature for a definite period. It was then decomposed by ice and HCl. Nitrobenzene was removed by steam distillation. The residual solid, if any, as well as the product obtained on cooling the liquid, were examined.

*(ii) Without a Solvent.*—The powdered ester was intimately mixed with aluminium chloride and the mixture heated to the required temperature for a definite period. It was then cooled; ice and HCl added and the solid obtained investigated.

The results of the various experiments are tabulated for the sake of brevity. In all the experiments, the reaction was carried out with 4.5 g. of coumarin ester for the sake of uniformity. Table I describes the Fries migration of the acetyl derivative and Table II describes the Fries migration of the benzoyl derivative under different conditions.

TABLE I  
Fries migration of 7-acetoxy-4-methylcoumarin

No.	Solvent.	Temp.	Time.	Amount of AlCl <sub>3</sub> (in moles)	Deacetylated 7-hydroxy-4-methyl-coumarin	Product-	
						7-Hydroxy-8-acetyl-4-methyl-coumarin (in g.)	7-Hydroxy-6-acetyl-4-methyl-coumarin (in g.)
1	Nitrobenzene (60 c.c.)	25-27°	24hr.	3.3	2.5g.	Indication	..
2	" (30 c.c.)	70°	6	1.1	3.0	..	..
3	" (60 c.c.)	70°	6	3.3	2.5	Traces	..
4	" (30 c.c.)	100°	4	1.1	3.0	..	..
5	" (60 c.c.)	"	4	3.3	2.0	0.5	..
6	" (30 c.c.)	130-40°	1	1.1	3.0	..	..
7	" (60 c.c.)	"	1	3.3	0.2	3.0	Traces
8	No solvent	"	1	1.1	3.0	..	..
9	"	"	1	2.2	3.0	..	..
10	"	"	1	3.3	0.5	2.5	Traces
11	Nitrobenzene (30 c.c.)	25-27°	24	1.1	3.0	..	..
12	" (50 c.c.)	"	24	2.2	3.0	..	..

1. No unreacted ester was recovered.

2. Amount of AlCl<sub>3</sub> used was 10% excess to account for inert ingredients

TABLE II  
Fries migration of 7-benzoyloxy-4-methylcoumarin

Solvent.	Temp.	Time	Amount of $AlCl_3$ (in moles)	Unreacted 7-benzoyloxy 4-methylcoumarin	Product.	
					Debenzoylated 7-hydroxy-4-methylcoumarin	7-Hydroxy-4-methyl-8-benzoylcoumarin
1 Nitrobenzene (60 c.c.)	25-27°	24 hrs.	3.3	2.5 g.	0.8g.	..
2 " (60 c.c.)	70	6	3.3	2.0	1.2	Indication
3 " (60 c.c.)	100	4	3.3	1.5	1.0	0.5g.
4 " (30 c.c.)	130-40	1	1.1	2.0	1.0	..
5 " (60 c.c.)	"	1	3.3	1.0	0.5	1.5
6 No solvent	"	1	3.3	1.2	0.7	1.0
7 Nitrobenzene (30 c.c.)	150-60	1	1.1	1.2	1.5	..
8 " (60 c.c.)	"	1	3.3	..	0.2	3.0
9 No solvent	"	1	1.1	2.0	1.0	..
10 " (30 c.c.)	"	1	3.3	..	0.4	2.5
11 Nitrobenzene (30 c.c.)	25-27	24	1.1	2.5	0.7	..
12 " (30 c.c.)	70	6	1.1	2.2	1.0	..

1. No 7-hydroxy-4-methyl-6-benzoylcoumarin could be isolated.

2. 7-Hydroxy-4-methyl-8-benzoylcoumarin gives dark red colouration with alcoholic ferric chloride characteristic of the compounds with -OH and -CO.R groups in *ortho*-positions. Limaye (*Ber.*, 1934, 67, 12; *Rasayanam*, 1937, 80) mentions that this compound does not give colouration with ferric chloride. This is probably due to the fact that this compound is sparingly soluble in alcohol.

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