THE FRIES REACTION

Part I. The Rearrangement of the Esters of Hydroxy Coumarins

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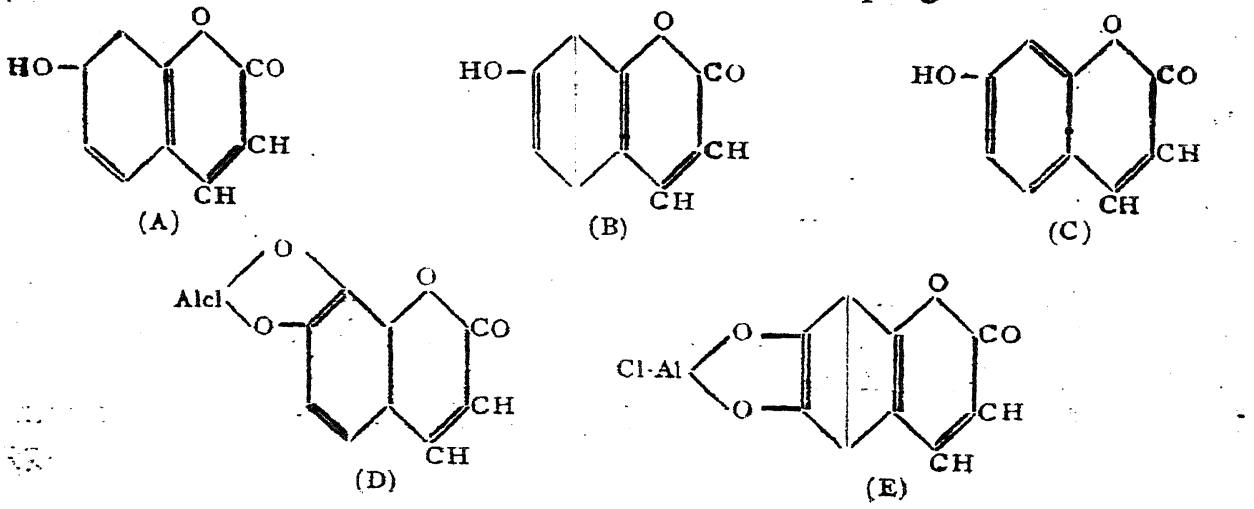
Received October 14, 1946

The Fries Reaction which is one of the convenient methods for the synthesis of hydroxyketones has been studied exhaustively with the esters of monohydric phenols, though much systematic work has not been done with those of polyhydric phenols. Among the esters of the hydroxy derivatives of heterocyclic compounds, some work has been done with the esters of hydroxy-Coumarins by various workers,[1] but not with a view to determining the effect of (*a*) temperature, (*b*) quantity of the aluminium chloride, (*c*) nature of the acyl group, (*d*) and the nature of the phenolic compound. Though our study has been mainly concerned with the last factor, *i.e.*, the effect exerted by the nature and position of the substituents present in the phenolic portion on the Fries migration, we have found that the most suitable temperature for the change is 150–160° C.; and the time period varying from one to one and a half hour. From our experience of the Fries migration of the esters of polyhydric phenols, we find that three mols. of aluminium chloride are required for one mol. of hydroxy-coumarins, while one mol. of dihydroxy coumarins requires four mols. of aluminium chloride. Nitrobenzene as a solvent is advantageous if the migration is to be studied at the ordinary temperature as a homogeneous solution is obtained. Less amounts of aluminium chloride leads to either deacetylation alone or partial migration. The acetyl group migrates more readily than the benzoyl group, but no comparative data has been studied.

7-acetoxy-coumarins were shown by Limaye (*loc. cit.*) to furnish 8-acetyl-7-hydroxy coumarins (main product) together with small quantities of 6-acetyl-isomers. If 8-acetyl-7-acetoxy-coumarins are taken, no Fries migration occurs, and deacetylation takes place, with the formation of the original 8-acetyl-coumarin. However, 6-acetyl-7-acetoxy coumarins give 6 : 8-diacetyl-7-hydroxy coumarins. The presence of alkyl groups in 6 or 8 positions do not interfere with this reaction. The diacetoxy derivatives of 7 : 8-dihydroxy coumarins and 6 : 7-dihydroxy coumarins undergo deacetylation only. 6-acetoxy-4-methyl coumarin, 6-acetoxy-4 : 7-dimethyl coumarin and 6-acetoxy-4-phenyl coumarin underwent deacetylation, while 6-acetoxy-7-methyl coumarin gave 6-hydroxy-5-acetyl 7-methyl coumarin;

thus showing that the inability of 6-acetoxy-4-methyl coumarins to undergo the reaction was due to steric hindrance by the substituent in 4 position. 5:7-diacetoxy-4-methyl coumarin underwent the Fries Reaction giving a mixture of 6:8-diacetyl-and 6 or 8-acetyl-5:7-dihydroxy-4-methyl coumarin. The acelates of 7-hydroxy-3:4-dialkyl, and 5-hydroxy-3:4-dialkyl-coumarins gave identical migration products as their parent compounds.

Limaye (*loc. cit.*) observed that 7-acetoxy-2-methyl-3-acetyl chromone underwent deacetylation. We found that 5-acetoxy-3-acetyl-2-methyl, and 6-acetoxy-3-acetyl-2-methyl chromones did not undergo this reaction, and only deacetylation took place. The above results could be explained on basis of the coumarin structure postulated by Rangaswamy and Sheshadri[2] as a result of the theory of the Fixation of Double-Bonds put forward by Mills and Nixon,[3] and the migration of the acyl group along the double bond from oxygen to the second carbon. Of the three possible forms (A, B and C), A is the most stable, but the possibility of B or C is not ruled out to explain the migration of the acyl group of 7-acetoxy-coumarins to position 6. To explain the non-migration of acyl groups in the case of 7:8-diacetoxy and 6:7-diacetoxy coumarins, the formation of ring compounds containing aluminium (D and E) are assumed. On these assumptions we could predict the positions which acyl groups would occupy when the acetoxy derivatives of the following unknown coumarins would be subjected to this reaction. 8-Acetoxy-coumarins would give 7-acyl-8-hydroxy-coumarins, while 5:6-diacetoxy coumarins would undergo deacetylation 5:8-diacetoxy-coumarins would give either 6-acyl-5:8-dihydroxy or 7-acyl-5:8-dihydroxy coumarins, while 6:8-diacetoxy-coumarins would yield 7-acyl-6:8-dihydroxy-coumarins, if the position 4 is also substituted. In case position 4 is unsubstituted they would furnish 5:7-diacyl-6:8-dihydroxy coumarins. Experiments to synthesise some of these unknown coumarins to test these views are in progress.



EXPERIMENTAL

The Fries migration of 7-acetoxy-8-ethyl-4: 5-dimethyl coumarin and formation of 7-hydroxy-6-acetyl-8-ethyl-4: 5-dimethyl-coumarin.—An intimate mixture of the coumarin (1 g.) and aluminium chloride (1·5 g.) was heated at 150-160 for 1½ hours. After decomposing the mixture with ice-cold water the solid crystallised from alcohol in needles m.p. 124° (yield = 0·5 g.). Its alcoholic solution gave red coloration with ferric chloride. (Found: C, 69·0; H, 6·4. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2 per cent.)

Condensation of 2-methylhydroquinone with malic acid and formation of 7-methyl-6-hydroxy-coumarin. The solution of the phenol (3 g.), and malic acid (5 g.) in 85 per cent. sulphuric acid (50 c.c.) was heated on water-bath for three hours, and was poured on ice. The solid crystallised from alcohol in colourless, lustrous needles m.p. 210° (yield = 45 per cent.). It dissolves in alkali with a pale yellow colour giving no fluorescence. (Found: C, 68·1; H, 4·6. $C_{10}H_8O_3$ requires C, 68·2; H, 4·5 per cent.)

The acetyl derivative crystallised from alcohol in colourless needles m.p. 151° C. (Found: C, 65·7; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6 per cent.)

Fries migration of 6-acetoxy-7-methyl coumarin, and Formation of 6-hydroxy-5-acetyl-7-methyl coumarin.—An intimate mixture of the above acetoxy coumarin (1 g.) and aluminium chloride (1·5 g.) was heated at 150°–160° for two hours. The product on crystallisation from benzene gave the first crop of 6-hydroxy-coumarin, while the mother-liquor on evaporation gave a solid which crystallised from alcohol in needles m.p. 152° (depressed by the original compound to 130–135°). Its alcoholic solution gave red coloration with ferric chloride (yield = 0·3 g.). (Found: C, 66·2; H, 4·7. $C_{12}H_{10}O_4$ requires C, 66·0; H, 4·6 per cent.)

The p-*nitrophenylhydrazone* of the above compound crystallised from alcohol in orange needles m.p. 272°. (Found: N, 12·0; $C_{18}H_{15}O_{15}N_3$ requires N, 11·9 per cent.)

Fries migration of 5:7-diacetoxy-4-methyl coumarin, and Formation of 6-or 8-acetyl-5: 7-dihydroxy coumarin and 6: 8-diacetyl-5: 7-dihydroxy-coumarin.—The Reaction was carried out as usual. The product (0·85 g.) on crystallising from alcohol gave two equal fractions: (1) Needles m.p. 298° which was identified as 6 or 8-acetyl derivative by direct comparison with an authentic specimen of Shah and Shah (*loc. cit.*); (2) Needles m.p. 164°, the alcoholic solution of which gave blackish red coloration with ferric chloride. It was found to be the 6:8-diacetyl derivative. (Found: C, 60·6; H, 4·5. $C_{14}H_{12}O_6$ requires C, 60·9; H, 4·3 per cent.)

Condensation of 1:2:4-*triacetoxy benzene with Ethy aceto-acelate and formation of* 6:7-*dihydroxy coumarin.*—This triacetoxy benzene was prepared by the action of acetic anhydride on *p*-benzoquinone according to the method of Thiele.[4] The solution of triacetoxy benzene (5 g.), and ethyl aceto-acetate (5 g.) in 73 per cent. sulphuric acid (25 c.c.) was kept overnight, and poured into water. The solid crystallised from alcohol in needles m.p. 269–270° which was 6: 7-dihydroxy-4-methyl coumarin.

The dimethyl ether obtained by methylating with dimethyl sulphate crystallised from dilute alcohol in needles m.p. 144°.

Hydrolysis of 6: 7-*dihydroxy-coumarin in presence of dimethyl sulphate and Formation of cis* 3: 4: 6-*tri-methoxy-B-methylcinnamic acid.*—To the solution of the coumarin (1 g.) in acetone (20 c.c.), dimethyl sulphate (10 c.c.) and sodium hydroxide (25 c.c. of 20 per cent. solution) was added, and the mixture refluxed on the water-bath, for one hour and a half. Further quantities of dimethyl sulphate (5 c.c.) and alkali (10 c.c.) were added. The cooled solution, on acidification with hydrochloric acid gave an acid which crystallised from dilute alcohol in lemon yellow, prismatic needles m.p. 150–151°. As the acid was unaffected by heat or light, and underwent cyclisation with concentrated sulphuric acid giving 6: 7-dimethoxy-4-methyl coumarin, it had the cis-configuration. (Found: C, 61·7; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3 per cent.

The diacetoxy-derivative of the coumarin) m.p. 134° (1g.) was converted into the original dihydroxy coumarin on heating with aluminium chloride (2 g.) at 150–160° for two hours.

We take this opprtunity of thanking the Rev. Father A. M. Coyne, S.J., for his kind interest in this work.

Summary

The Fries Reaction of some 7-acetoxy,-6-acetoxy,-7: 8-diacetoxy and 6: 7-diacetoxy coumarins has been studied, and explanation has been given for the failure as well as the success of the reaction.

References

1. Limaye and Co-workers .. *Ber.* 1932, **65**, 12.
.. *Rasayanam*, 1936, **20**; 1937, **93**; 1938, **141**; 1939, **187**.
Shah and Co-workers .. *J. C. S.*, 1938, **228**, 1424.
Deliwalla and Shah .. *Ibid.*, 1939, 1250.
Desai and Co-workers .. *Proc. Ind. Acad. Sci.*, (A), 1937, **6**, 185; 1938, **8**, 571; 1941, **14**, 99; 1942, **15**, 11.
Rao and Sheshadri .. *Ibid.*, 1940, **11**, 208.
Shah and Thakor .. *J. Ind. Chem. Soc.*, 1946, **14**, 199.
2. Rangaswamy and Seshadri .. *Proc. Ind. Acad. Sci.*, 1941, **14**, 562.
3. Mills and Nixo .. *J. C. S.*, 1930, 2510.
4. Thiele .. *Ber*, 1898, 1247.