SYNTHETIC EXPERIMENTS IN THE BENZO-PYRONE SERIES

Part VIII. Some Transformations of 5-Hydroxy-Coumarin Derivatives

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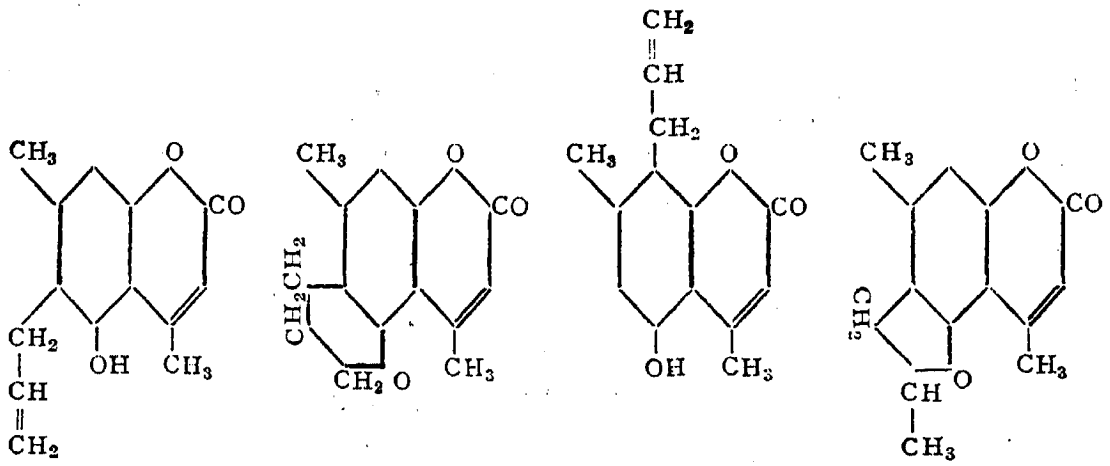
OF the two types, 7-hydroxy- and 5-hydroxy-coumarins, the former have been more fully examined in the past obviously due to their common occurrence in nature and the greater ease with which they can be prepared by synthetic methods. In connection with our work on insecticides more information was required about 5-hydroxy-coumarin derivatives and the results presented in this paper were obtained in that connection. There is considerable difference between the two types of compounds and their derivatives. The 7-hydroxy-compounds exhibit marked fluorescence in solution whereas the 5-hydroxy-compounds are entirely devoid of this characteristic. They also differ in their solubility in mild alkalies, the 5-hydroxy-compounds being less soluble.

The Claisen and Fries transformations of 7-hydroxy-coumarin derivatives have been investigated in detail in the past. The allyl ethers do not readily undergo transformation below 200° and the best yields are obtained by heating between 210–240°. In general they rarely exceed 30%, due to the formation of considerable amounts of resins. Of the two alternative ortho-positions (6 and 8) available for the migration, the 8-position seems to be almost exclusively involved, since only 8-allyl-7-hydroxy-coumarins have so far been obtained.[1] On the other hand when the acetate is subjected to Fries migration a small amount of the 6-acetyl-derivative is also obtained though the main bulk of the product is the 8-substituted compound.[2] In regard to the 5-hydroxy-coumarins the positions that could be involved in the above transformations are 6 and 8, the former being ortho and the latter para to the original hydroxyl group. The transformation of the allyl ethers in this type of compounds has not so far been described. Fries migration has been studied by Shah[3] and by Limaye[4] in the case of the acetate of 4-methyl-

5-hydroxy coumarin and they have been able to obtain only the 6-acetyl-derivative. This is rather extraodinary since it is generally considered that in the Fries transformation para migration takes place more easily than the ortho.

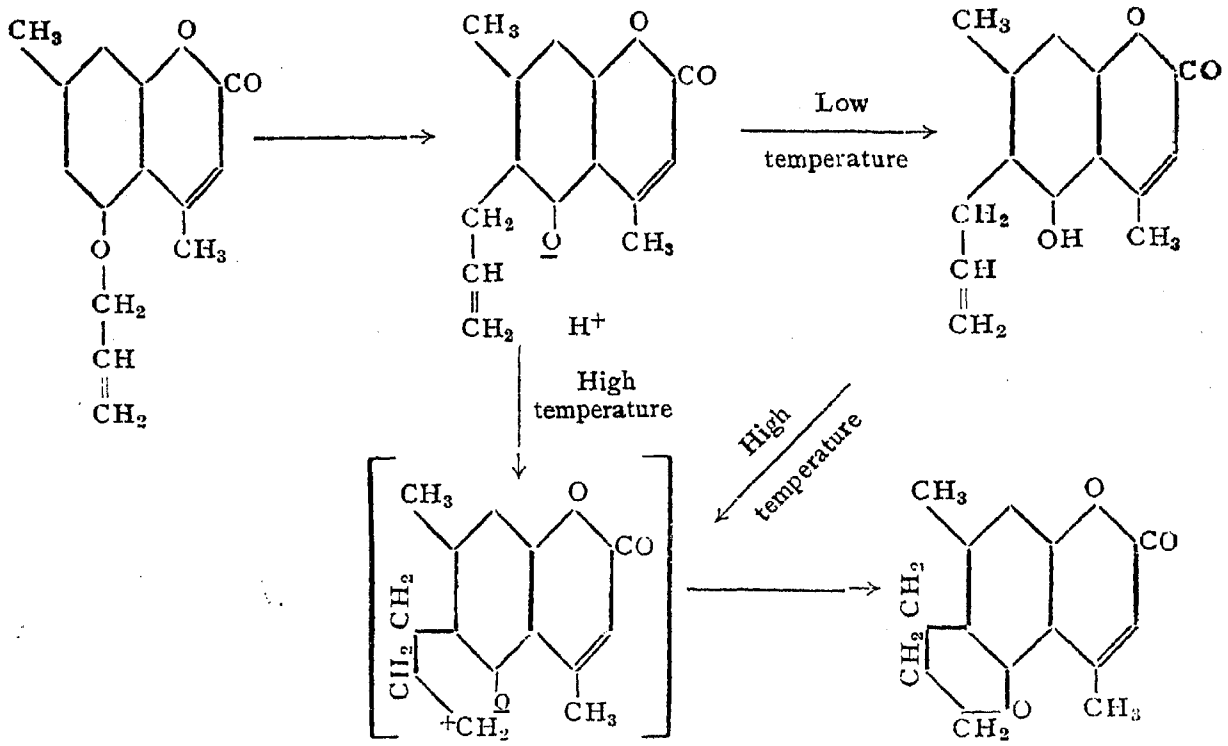
As a typical example of 5-hydroxy-coumarins, 5-hydroxy-4·7-dimethyl-coumarin has now been chosen since it is readily made from orcinol and ethylacetoacetate by the well-known Pechmann condensation. It was originally prepared by Pechmann and Cohen[5] who thought it was a 7-hydroxy-compound in analogy with 4-methyl umbelliferone obtained from resorcinol. It however does not give the characteristic fluorescence of umbelliferone derivatives. Its correct constitution as a 5-hydroxy-compound was later eatablished by Dey.[6] Its allyl ether gives rise to different products depending upon the temperature employed for the migration. When heated at 160–5° C. (lower temperature) for about 2 hours it forms in a very high yield an alkali-soluble product (I) having all the properties of an allyl phenol and a melting point of 178–9°. But if the migration is carried out at a higher temperature (195–200°) at atmospheric pressure or *in vacuo* an alkali insoluble substance (II) is formed as the entire product and it melts at 164–5°. When the experiment is carried out at 225–30° two products are obtained the alkali-insoluble substance (II) which is the major component and an alkali-soluble substance (III) melting at 239–40°. All the three are isomeric and from their reactions and properties it could be concluded that compound (I) is 6–allyl-5-hydroxy-4 : 7-dimethyl-coumarin, compound (II) has a ring structure produced by interaction between the hydroxyl and the ethylene double-bond and compound (III) is the para isomer of (I), that is 8 allyl-5-hydroxy-4 : 7-dimethyl-coumarin. In support of this idea it has been found by heating (I) again at 215–20°, a substance identical with (II) could be obtained. It could therefore be concluded that when higher temperatures are employed for migration both the 6-(I) and 8-allyl (III) compounds are formed, the former immediately undergoing cyclisation to yield (II); this change is not possible with the 8-allyl compound.

The alkali-insoluble substance appears to be a single entity since repeated recrystallisation and fractionation has given rise to only one product with a constant melting point. There are two possible structures for this compound the chroman (II) and the methyl-coumaran (IV). In order to settle this point the methyl-coumaran has been prepared from (I) by adopting the procedure of Adams *et al.*[7] (using mercuric chloride) as modified in a recent publication by Krishnaswamy and Seshadri.[8] Since it is quite different from the alkali-insoluble product obtained by Claisen transformation the latter has been assigned the chroman structure (II)



(I) (II) (III) (IV)

The above results are interesting in many respects. While carrying out the pyrolytic rearrangement of phenylallyl ether into *o*-allyl-phenol, Claisen[7a] observed that a small amount of 2-methylcoumaran was formed. The yield of this could be raised to 60% by employing acids or salts as catalysts. In connection with synthetic work relating to vitamin E,[9] it was found that ring closure of ortho-allylphenols derived from ψ-cumoquinol in the presence of catalysts is dependent on the nature of the side-chain. With a simple allyl group methyl-coumaran was produced, whereas with dimethyl-allyl and phytyl groups the chroman was formed. The crotyl group was an intermediate case giving rise to a mixture of both. Subsequently Hurd and Hoffmann[9a] showed that with the simpler phenols having allyl and crotyl groups it is possible to get either the coumaran or the chroman ring by suitably adjusting the conditions. In the absence of peroxides the coumarans were produced and in their presence chromans were formed. With dimethyl-allyl group the chroman was produced even without a peroxide. The results reported in the present paper indicate the existence of another possibility where even the simple allyl group can give rise to a chroman in the absence of peroxide or catalyst probably due to the influence of the 5-hydroxy-coumarin structure already present. Obviously in these reactions the nature of the product is dependent on a number of factors (I) the structure of the original phenolic body, (2) the nature of the allyl side chain and (3) the presence or absence of peroxides. It should be mentioned here that almost quantitative yields of the coumarino-chroman are obtained when it is directly made from the allyl ether as contrasted with the partial transformation of the 6-allyl-5-hydroxy coumarin (yield 30%). Obviously the 6-allyl compound is not an intermediate stage between the allyl ether and the chroman in the direct process. The following mechanism could probably represent the changes correctly.

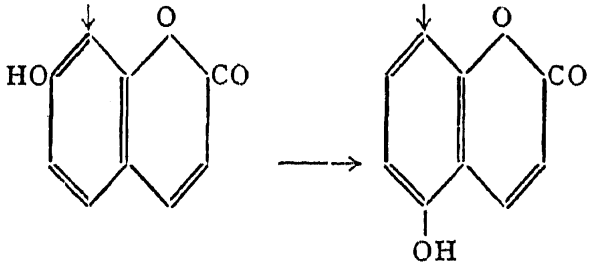


In order to ascertain whether the peculiarities mentioned above are innate characteristics of the 5-hydroxy-compound or are due to the effect of the methyl group coming from the orcinol part, the Claisen migration of the allyl ether of 7-hydroxy-5-methyl-coumarin, a condensation product of orcinol and malic acid,[5a] has also been studied. The results are quite analogous to those of umbelliferone derivatives and the methyl group of the orcinol nucleus has no special effect. The migration does not take place at a lower temperature (170°) and at a higher temperature (200°) only 8-allyl-7-hydroxy-5-methyl-coumarin is obtained in comparatively small yields. There is thus marked difference between 7-hydroxy and 5-hydroxy-coumarins in the nature of the claisen migration of the corresponding allyl ethers. The former undergo change only at a higher temperature and the yields of the allyl phenols are poor, probably due to polymerisation taking place side by side yielding resins. The latter undergo the migration easily and give good yields of products, the nature of which depend upon the temperature employed.

The Fries migration of 5-acetoxy-4: 7-dimethyl coumarin has also been examined now. The product yields only one crystalline compound whose properties and reactions indicate that it is the 6-acetyl derivative; migration to the 8-position does not seem to have taken place to any appreciable extent and in this there is agreement with the behaviour of 5-acetoxy-4-methyl coumarin. The exclusive formation of the 6-acetyl-compound as the result of Fries reaction of 5-hydroxy-coumarin-acetates may probably

be attributed to the high temperature that has necessarily to be employed in the case of these compounds in order to get them fused with aluminium chloride. High temperature has been found to favour in other cases also ortho migration in preference to the para[10].

The difference in the behaviour of 7-hydroxy and 5-hydroxy coumarin derivatives in Claisen and Fries migrations may be partly due to the fact that in the former only ortho positions are available for reaction and in the latter an ortho and a para position. Similar differences exist in nitration also. In 7-hydroxy-coumarin the 8th position is consistently very highly reactive as compared with the feeble reactivity of position 6 in all reactions. This was attributed by Rangaswamy and Seshadri[11] to the preferential orientation of a double-bond between the 7th and 8th positions (formula V). In 5-hydroxy coumarins position 6 (ortho) has been shown to be reactive in Claisen and Fries migrations. Working with 5-hydroxy-4-methyl-coumarin Parekh and Shah[12] found that nitration at 0° C. gave the 8-nitro compound (*p*-nitration) whereas at the room temperature 6 : 8-dinitro compound was produced. Obviously ortho or para reactivity in 5-hydroxy coumarins is controlled by the nature of the entering group and the conditions. The formula (V) satisfactorily explains all the properties of 5-hydroxy coumarins also. A para position can be activated in any disposition of the double bonds in the benzene ring. Hence in studying the possible fixation of double bonds two rival ortho positions alone seem to offer possibilities of correct comparison and not an ortho and a para combination; 5-hydroxy coumarins do not seem to be, therefore, suitable for this study.



(V *a*) (V *b*)

Experimental

5-*Hydroxy*-4 : 7-*dimethyl-coumarin*.—This compound was obtained in very good yields by keeping overnight a mixture of equimolecular proportions of orcinol and ethylacetoacetate and twice their combined weight of concentrated sulphuric acid and working it up the following day (2·8 g. of coumarin from 2·0 g. of orcinol).

It could also be obtained in equally good yields by heating the mixture in the above proportions in a boiling water-bath for 1 hour.

Appel's method using anhydrous alcoholic solution and saturating it with dry hydrogen chloride gave the product in good yields but the method is not very convenient.

5-*Allyloxy*-4 : 7-*dimethyl-coumarin*.—5-Hydroxy-4 : 7-dimethyl-coumarin (9·5 g.) and allyl bromide (6·0 g.) were dissolved in anhydrous acetone (400 c.c.), anhydrous potassium carbonate (20 g.) added and the mixture boiled under reflux on a water-bath for about 6 hours. The acetone was then removed by distillation and water added to the residue. The insoluble solid was filtered and recrystallised from alcohol; the allyl ether was thus obtained as rectangular plates melting at 127–8°; yield almost quantitative. (Found: C, 73·3; H, 6·4; $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%.)

Claisen migration: (i) 6-*Allyl*-5-*hydroxy*-4: 7-*dimethyl-coumarin*.—The allyl ether (2 g.) was heated for 2 hours in a paraffin-bath, the temperature of which was maintained at 160–5°. The product was then mostly soluble in aqueous sodium hydroxide. The alkali solution on acidifying yielded a precipitate, which on recrystallisation from alcohol, was obtained as colourless elongated rhombohedral crystals, melting at 178–9°. The substance gave no prominent colour with ferric chloride; yield 1·5 g. (Found: C, 73·2; H, 6·4; $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%.)

(ii) *a*. 4: 7-*Dimethyl-coumarino*-5: 6-*chroman*.—The allyl ether (5 g.) was heated in a paraffin-bath at 225–30° for 2 hours. The final product was separated into an alkali-soluble fraction and an alkali-insoluble fraction. The latter on recrystallisation from alcohol gave rectangular plates, melting at 164–5°; yield 4·0 g. (Found: C, 73·1; H, 6·4; $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%.)

b. 8-*Allyl*-5-*hydroxy*-4: 7-*dimethylcoumarin*.—The alkali-soluble fraction obtained in the above experiment was liberated by acidifying the alkaline solution. The precipitate thus obtained on recrystallisation from alcohol yielded colourless rectangular plates and prisms, melting at 239–40°; yield 0·2 g. (Found: C, 72·7; H, 6·5; $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%.)

The above chroman could also be obtained in almost quantitative yields by heating the allyl ether (2 g.) at 195–200° either at atmospheric pressure in an evacuated system (water-pump) but no 8-allyl-compound could solated in these cases.

iii) The 6-allyl compound obtained in (I) (1 g.) was heated at 215–20° affin-bath for 2 hours. It was then separated into an alkali-soluble and an alkali-insoluble fraction. The alkali-soluble portion after

repeated purification was found to be identical with the original 6-allyl-compound (melting at 178–9°). The alkali-insoluble portion on re-crystallisation from alcohol was obtained as rectangular plates, melting at 163–4°; (yield 0·3 g.); the mixed melting-point with chroman obtained in (ii *a*) was undepressed.

Mercuric chloride addition compound of 6-allyl-5-hydroxy-4: 7-dimethyl coumarin.—To a solution of 6-allyl-5-hydroxy-4: 7-dimethyl-coumarin (2 g.) in methyl alcohol (20 c.c.), a solution of mercuric chloride (2·5 g.) in the same solvent (20 c.c.) was added and the mixture left overnight. The mercuric chloride addition product crystallised out in rectangular rods. The pure sample obtained by washing the precipitate with a little alcohol melted at 228–9°; yield 3·5 g. (Found: Cl, 14·0; $C_{14}H_{14}O_3$, $HgCl_2$ requires Cl, 14·2%.)

4: 7-*Dimethyl coumarino-α-iodomethyl-dihydro-5: 6-furan.*—The mercuric chloride addition compound (3 g.), was ground up with excess of a solution of iodine in potassium iodide solution; the reaction was facilitated by warming the mixture on a water-bath for about an hour. The precipitate was then filtered and recrystallised from alcohol. It was then obtained as rectangular prisms, melting at 166–7°; yield almost quantitative. (Found: I, 35·1; $C_{14}H_{13}O_3$ I requires I, 35·7%.)

4: 7-*Dimethyl-coumarino-α-methyl-dihydro-5: 6-furan.*—The iodine compound (2·5 g.) was suspended in alcohol (50 c.c.) and small pieces of sodium metal were pressed to the bottom of the container by means of a glass rod. The addition of sodium was continued till the reaction became very slack. The solution was then diluted with water and acidified. On standing, a precipitate was obtained, which on recrystallisation yielded colourless rectangular plates melting at 205–6°; yield 0·2 g. The substance is insoluble in hot dilute sodium hydroxide. (Found: C, 73·3; H, 6·4; $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%.)

7-*Allyloxy-5-methyl coumarin.*—7-Hydroxy-5-methyl coumarin[6a] was allylated as in the previous case using allyl-bromide and anhydrous potassium carbonate in acetone medium. The allyl ether crystallised out from alcohol in rectangular plates, melting at 78–9°; yield quantitative. (Found: C, 72·4; H, 5·8; $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%.)

8-*Allyl-7-hydroxy-5-methyl-coumarin.*—The above compound (2 g.) was heated in an oil-bath at 200–5° for about 2 hours. The product thus obtained was found to be almost completely soluble in aqueous sodium hydroxide. The clear solution was acidified and the precipitate obtained therefrom repeatedly recrystallised from alcohol. The allyl phenol was

thus obtained in rectangular plates, melting at 174–5°; yield 0·6 g. (Found: C, 71·8; H, 5·2; $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·6%.)

The Claisen migration was also carried out at a higher temperature (230–40°). The yield of the allyl phenol was considerably lower than in the previous case due to greater resinification but no chroman could be isolated.

4: 7-*Dimethyl-5-acetoxy-coumarin*.—It was prepared by heating together a mixture of 5-hydroxy-4: 7-dimethyl-coumarin, acetic anhydride and anhydrous sodium acetate. On recrystallisation from alcohol the acetate was obtained as rectangular plates, melting at 199–200° (*cf.* Pechmann[3], 195°).

Fries migration of the acetate: *preparation of* 6-*acetyl*-5-*hydroxy*-4: 7 *dimethyl coumarin*.—The acetate (3 g.) and anhydrous aluminium chloride (6 g.) were powdered together and heated in an oil-bath at 130° at first and the temperature was slowly raised to 170° during the course of half-an-hour. The heating was continued at this temperature for an hour more. The material was then cooled and aluminium chloride was dissolved out using dilute hydrochloric acid. The solid left behind was filtered and recrystallised from glacial acetic acid. 6-Acetyl-5-hydroxy-4: 7-dimethyl-coumarin was thus obtained as rectangular plates, melting at 177–8°. By repeated crystallisation and fractionation no change was effected in the melting point and no other product could be isolated. This substance gives a marked brown colour with ferric chloride indicating the presence of an ortho-hydroxy-carbonyl grouping in it. Yield 1·0 g. (Found: C, 67·6; H, 5·4; $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%.)

Summary

Claisen migrations of the allyl ether of 4: 7-dimethyl-5-hydroxy-coumarin gives rise to three isomeric compounds depending upon the conditions, (I) 6-allyl-5-hydroxy-4: 7-dimethyl coumarin (high yield), (II) the corresponding chroman (high yield), and (III) 8-allyl-5-hydroxy-4: 7-dimethyl coumarin (low yield). (II) has been shown to be a chroman by comparison with the corresponding methyl coumaran obtained by authentic methods from (I). The acetate of the above coumarin undergoes Fries reaction to give the 6-acetyl compound. Claisen migrations of the allyl ether of 7-hydroxy-5-methyl-coumarin yields only the 8-allyl-derivative. The difference in the behaviour of the derivatives of 5- and 7-hydroxy coumarins and the special conditions of the chroman and coumaran ring closure of *o*-allyl phenols are discussed.

REFERENCES

1.	Baker and (Miss) Lothian		*J. C. S.*, 1935, 628.
2.	Limaye	..	*Ber.*, 1932, 375.
3.	Shah *et al.*	..	*J. C. S.*, 1938, 228.
4.	Limaye *et al.*	..	*Rasayanam*, 1938, 153.
5.	Pechmann and Cohen	..	*Ber.*, 1884, **17**, 2188.
5*a*.	—— and Welsh	..	*Ibid.*, 1884, **17**, 1649.
	Rao and Seshadri	..	*Proc. Ind. Acad. Sci.*, A, 1941, **13**, 255.
6.	Dey	..	*J. C. S.*, 1915, 1614.
7.	Adams *et al.*	..	*J. A. C. S.*, 1922, 1781.
7*a*.	Claisen *et al.*	..	*Ann. der chemic*, 1913, **401**, 21.
8.	Krishnaswamy and Seshadri		*Proc. Ind. Acad. Sci.*, A, 1941, **13**, 43.
9.	Karrer *et al.*	..	*Helv. Chim. Acta*, 1939, 1287.
9*a*.	Hurd and Hoffman	..	*J. Org. Chem.*, 1940, **5**, 212.
10.	Blatt	..	*Chem. Rev.*, 1940, **27**, 417.
11.	Rangaswami and Seshadri		*Proc. Ind. Acad. Sci.*, A, 1937, **6**, 122.
12.	Parekh and Shah	..	*J. I. C. S.*, 1942, 335.