HETEROCYCLIC COMPOUNDS.

Part III. The Synthesis of Cyclopenteno-(1': 2': 2 : 3)-chromones, and a Discussion on the Mechanism of the Pechmann and the Simonis Reactions.

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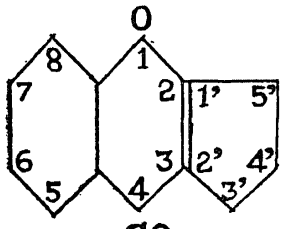
The condensation of phenols with open-chain β-ketonic esters in the presence of concentrated sulphuric acid, usually known as the Pechmann Reaction[1] has been a prolific source of the synthesis of substituted coumarins or 1 : 2-benzopyrones. Later on, Simonis[2] showed that this reaction could be made to give chromones or 1 : 4-benzopyrones by substituting phosphorus pentoxide for concentrated sulphuric acid. Jacobson and Ghosh,[3] on the other hand, reported the formation of chromones in the Pechmann Reaction, when one of the hydrogens of the reactive methylene group of the β-ketonic ester was replaced by a sufficiently bulky group. Unfortunately, all the alleged chromones were proved to be coumarins by Baker and Robinson,[4] and, therefore, there existed considerable doubt if chromones could at all be produced by the Pechmann Condensation. However, the isolation of a chromone in the condensation of acetoacetic ester with β-naphthol in the presence of concentrated sulphuric acid by Dey and Lakshminarayanan[5] has shown the existence of this possibility, though it must be admitted that this is the only observation of its kind.

The Simonis Reaction itself has been the subject of an exhaustive and critical investigation independently by Robertson[6] *et al.* as well as D. Chakravarti[7] and his co-workers. Robertson came to the conclusion which he recanted afterwards that the chromone formation depended mainly on the character of the phenol. Chakravarti is of opinion that the formation of the chromone is governed by the nature of the phenols as well as the β-ketonic esters. Only those phenols which do not undergo the Pechmann Reaction or do it reluctantly give chromones. With regard to the β-ketonic esters, alkyl groups in the α-position favour chromone formation. Phosphorus pentoxide is the only condensing agent which promotes the chromone formation when other favourable conditions are present, the only exception being the case noted by Dey and Lakshminarayanan (*loc. cit.*).

As literature showed the absence of work on the formation of chromones from phenols and cyclic β-ketonic esters, we took up this investigation to see how these esters compare themselves with their open-chain analogues with regard to the Simonis Reaction. We have been able to prepare chromones from phenol, *m*-cresol, *p*-cresol and β-naphthol by condensing them with ethyl-cyclopentanone-2-carboxylate in the presence of phosphorus pentoxide. Phosphorus oxychloride which has been recently recommended by Robertson *et al.* (*loc. cit*) for this purpose is not as convenient as phosphorus pentoxide because of the formation of tarry and coloured by-products. Following the nomenclature[8] of the coumarins, we have named the chromone from ethyl cyclopentanone-2-carboxylate and phenol as cyclo-penteno-(1' : 2' : 2 : 3)-chromone or cyclopenteno-(1' : 2' : 2 : 3)-1 : 4 benzo-pyrone (I). These chromones condense with aldehydes with the formation of styryl derivatives as noticed by Chakravarti, Heilbron and others,[9] and are soluble in HCl (I : I). Their melting points and mixed melting points with the isomeric coumarins described by the authors in Part I of this series leave no ambiguity regarding their structure which is finally confirmed by their alkaline hydrolysis into ketones and *o*-hydroxy-acids (II). These chromones thus offer a marked contrast to the isomeric coumarins which are stable to alkaline hydrolysis, and simulate the behaviour of tetrahydro-xanthone synthetically prepared by M. Sen.[10]



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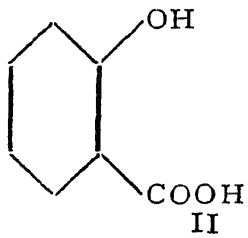
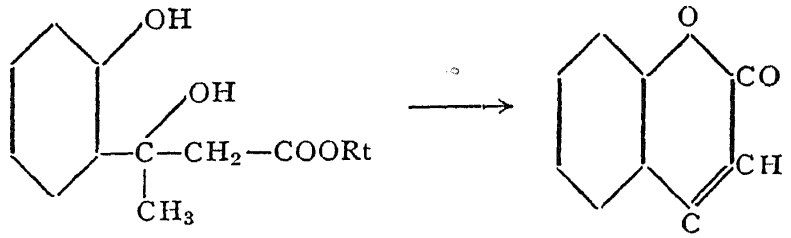


II

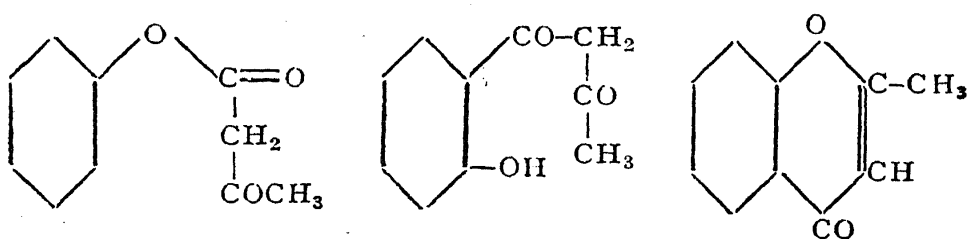
The formation of coumarins in the Pechmann Reaction has always been cited as a proof of the enolic nature of β-ketonic esters. The effect of substituents in the α-position of the β-ketonic esters will be to enhance or retard the enolisation, and experimental evidence bears out that substituents like halogens which tend to increase the tendency for enolisation give better yields of coumarins, while the opposite effect is observed in the case of alkyl groups which will suppress enolisation. This explanation is quite plausible so far as the part played by the ester is concerned, but it does not take count of the rôle played by the phenol. The alternative explanation which is worthy of consideration is, that the reactive hydrogen of the phenols which undergo the Pechmann Reaction co-ordinates itself readily with the carbonyl group of the ketonic ester. This hydrogen must always be in the *ortho*-position to the phenolic hydroxyl group and should

be sufficiently reactive, otherwise the tendency for the formation of the additive product will be either small or nil. The additive product (III) which is thus first formed, undergoes dehydration and cyclisation to coumarins. Any dehydrating agent can function as a condensing agent, and this is the reason why many condensing agents have been found serviceable in the Pechmann Reaction, though they differ among themselves with regard to their efficiency. The substituent in the β-ketonic ester will either facilitate or retard the formation of the additive product (III), and the effect will be partly polar and partly steric.



III

The mechanism of the Simonis Reaction is fundamentally different. By this reaction, we mean the interaction of phenols and β-ketonic esters in the presence of phosphorus pentoxide with the formation of chromones only. Chakravarti (*loc. cit.*) has already observed that those phenols which do not contain a reactive hydrogen *ortho* to the hydroxyl group give the chromones in this reaction. Therefore, it is plausible to assume that the reactive hydrogen in the case of the phenols which undergo the Simonis Reaction belongs to the hydroxyl group which interacts with the β-ketonic esters giving the aryl esters of these acids. These aryl esters undergo an isomeric change analogous to the Fries Transformation with the formation of *o*-hydroxy-benzoyl-acetylmethane (V) which is dehydrated to 2-methyl-chromone (VI). The specific condensing action of phosphorus pentoxide may be in facilitating the formation of either (IV) or (V) or both, as the conversion of (V) into (VI) may be accomplished with the help of any dehydrating agent. The intermediate formation of *o*-hydroxy-aroylacetyl-methanes in the Kostanecki Reaction has been proved by Baker,[11] and we are of opinion that this stage is also produced in the course of the Simonis Reaction. We have already some experimental work on hand to test the assumptions made, as well as to synthesise the chromones from other cyclic β-ketonic esters and phenols.



Experimental.

Cyclopenteno-(1' : 2' : 2 : 3)-*chromone.*—An intimate mixture of phenol (2 g.), ethylcyclopentanone-2-carboxylate (2 g.) and phosphorus pentoxide (5 g.) was heated in a round bottom flask on a water-bath for three hours. The cooled mass was treated with water and warmed up for some time, cooled, extracted with ether, and the ethereal extract washed twice with an excess of 5 per cent. caustic soda solution, dried, and the solvent recovered. The residue deposited crystalline needles on standing in a vacuum, and these were carefully washed with ether to remove the gummy impurities and finally crystallised from ether, when white needles (m.p. 120°) were obtained and the m.p. was depressed to 90° by admixture with the isomeric coumarin (m.p. 129°). (Found : C, 77·0 ; H, 5·4 ; $C_{12}H_{10}O_2$ requires C, 77·4 ; H, 5·4 per cent.)

The chromone is easily soluble in alcohol, acetic acid, acetone, benzene, ether, etc., but almost insoluble in petrol.

The *styryl derivative* was prepared by keeping overnight the alcoholic solution of the chromone (0·5 g.), benzaldehyde (0·5 g.) and sodium ethoxide (0·5 g. Na in 10 c.c. abs. alcohol). The solid was filtered off, and crystallised from alcohol in white needles (m.p. 161°). (Found : C, 83·1; H, 5·2; $C_{19}H_{14}O_2$ requires C, 83·2 ; H, 5·1 per cent.)

Alkaline hydrolysis.—The chromone (0·2 g.) was heated with N.NaOH (10 c.c.) for two hours on a sand-bath under reflux. After dilution with water, the alkaline solution was extracted with ether, and acidified with concentrated HCl. The acid obtained on cooling melted at 155°, and was identified as salicylic acid by comparison with an authentic specimen.

6-*Methylcyclopenteno*-(1' : 2' : 2 : 3)-*chromone.*—A mixture of *p*-cresol (3 g.), the ester (4 g.) and phosphorus pentoxide (6 g.) was heated on a water-bath for six hours and then at 130°–140° for one hour. The insoluble residue left after decomposing the mass with water was taken up in ether and the solution washed completely with alkali to remove the phenol, dried and the solvent recovered. On keeping in a vacuum the chromone solidified, and the solid then crystallised from ether in colourless needles (m.p. 144°). The isomeric coumarin melts at 174°. It resembled the parent substance in solubility and was hydrolysed by alkali to 2-hydroxy-5-methyl-benzoic acid[12] (m.p. 150°). (Found : C, 77·8 ; H, 6·1 ; $C_{13}H_{12}O_2$ requires C, 78·0 ; H, 6·0 per cent.)

7-*Methyl-cyclopenteno*-(1' ; 2' : 2 : 3)-*chromone.*—An intimate mixture of the ester (3 g.), *m*-cresol (3 g.) and phosphorus pentoxide (6 g.) was heated on a water-bath for half an hour, and then at 130°–140° for another half an

hour. The mixture which charred and swelled appreciably was decomposed with water and the insoluble portion taken up in ether, washed with alkali-dried, and the solvent recovered. The residue which solidified after some time in a vacuum crystallised from ether-petrol (b.p. 40°–60°) mixture in colourless needles (m.p. 83°–84°). The isomeric coumarin melts at 105°. It was hydrolysed by alkali to 2-hydroxy-4-methyl-benzoic acid[13] (m.p. 175°). (Found : C, 77·9 ; H, 6·3 ; $C_{18}H_{12}O_2$ requires C, 78·0 ; H, 6·0 per cent.)

Cyclopenteno-(1' : 2' : 2 : 3)-1 : 4-*βα-naphtha-pyrone.*—A mixture of the ester (3 g.), β-naphthol (3 g.) and phosphorus pentoxide (6 g.) was heated on the water-bath for three hours, and at 120° for further half an hour. After treatment with water, the gummy residue was extracted with ether, the solution thoroughly washed with 5 per cent. alkali, dried, and the solvent recovered. The semi-solid mass thus obtained crystallised from alcohol in colourless needles (m.p. 165°–166°). The isomeric coumarin could not be prepared. (Found : C, 81·3 ; H, 4·9 ; $C_{16}H_{12}O_2$ requires C, 81·4 ; H, 5·1 per cent.) Its alkaline hydrolysis gave 2-hydroxy-α-naphthoic acid[14] (m.p. 156°) (rapid heating).

The styryl derivative, which was easily obtained by the usual method, crystallised from alcohol in very pale-yellow silky needles (m.p. 220°). (Found : C, 85·0 ; H, 5·1 ; $C_{23}H_{16}O_2$ requires C, 85·2 ; H, 4·9 per cent.)

We have great pleasure in thanking Dr. R. F. Hunter for his kind interest in this work.

Summary of Part III.

Chromones have been prepared by condensing cyclopentanone-2-carboxylate with phenol, *m*-cresol, *p*-cresol and β-naphthol in the presence of phosphorus pentoxide. The mechanism of the Pechmann and Simonis Reactions has been discussed.

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