CONSTITUTION OF COUMARINOPYRONES DERIVED FROM 7-HYDROXY-COUMARINS.

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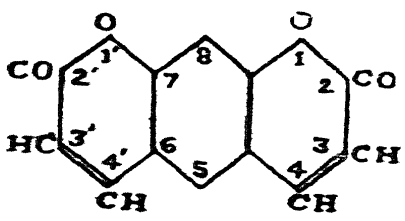
During the preparation of 4-methylumbelliferon from resorcinol and ethylacetoacetate using alcoholic hydrogen chloride as the condensing agent it was noticed by us that it was always accompanied by more or less quantities of a complex, sparingly soluble substance. This could be crystallised from hot acetic acid or pyridine and was found to be identical with 4 : 4′-dimethylcoumarinopyrone first prepared in a very small yield by Hantzsch and Zürcher[2] from resorcinol (1 mol.) and ethylacetoacetate (2 mols.) using sulphuric acid as the condensing agent. It has been obtained in better yields more recently by Sen and Chakravarti[3] by condensing 4-methylumbelliferon with ethylacetoacetate in the presence of sulphuric acid. This condensation of 4-methylumbelliferon does not succeed with alcoholic hydrogen chloride which however produces a good yield of the coumarinopyrone by the direct reaction of resorcinol and ethylacetoacetate.

Besides obtaining the above dimethylcoumarinopyrone, Sen and Chakravarti have condensed a few other umbelliferon derivatives with malic acid and ethylacetoacetate and obtained the corresponding coumarinopyrones. The exact constitutions of these compounds were left undecided by them. There are two alternatives for the formation of the new pyrone ring. The compound may be the linear coumarino-7 : 6-α-pyrone (I) or the angular coumarino-7 : 8-α-pyrone (II). Since this question is closely connected with work in progress in these laboratories, an attempt has now been made to settle it in as unambiguous a manner as possible.



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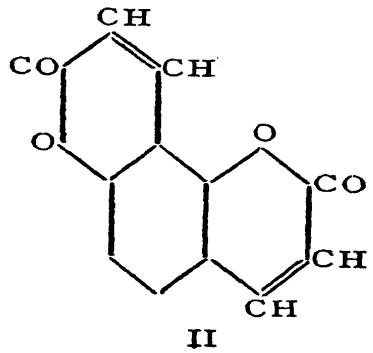

II

The above compounds have received different names at different times. Hantzsch and Zürcher's name 'dicoumarins' is obviously unsuitable. Sen and Chakravarti called them 'coumaropyrones'. Under this name they are likely to be mistaken for coumarone compounds, a large number of which occur frequently in nature. Hence they are now named 'coumarino-α-pyrones'. The positions in the coumarin ring are numbered as usual from 1 to 8 and those in the second pyrone ring are marked with a dash. As will be easily evident from a scrutiny of the two isomers there is only one possible way of naming the linear compound which is symmetrical, whereas there are two possible names for the angular variety as (1) coumarino-7 : 8-α-pyrone or (2) coumarino-5 : 6-α-pyrone.

Umbelliferon was converted into 7-hydroxycoumarin-8-aldehyde by Späth and others[4] using hexamethylenetetramine and its constitution was established by them by synthesising angelicin from it. This aldehyde has now been subjected to the Perkin's condensation using sodium acetate and acetic anhydride giving rise to coumarino-7 : 8-α-pyrone (II). The aldehyde of 4-methylumbelliferon has been made by adopting the same method. By analogy this could be assumed to be the 8-aldehyde. But we have made the constitution surer by reducing it with hydrogen in the presence of palladium-charcoal to the corresponding methyl derivative. This had been found to be identical with 4 : 8-dimethyl-7-hydroxycoumarin which could be synthesised from 2-methylresorcinol by condensation with ethylacetoacetate by the Pechmann's method. The aldehyde, therefore, becomes 4-methyl-7-hydroxycoumarin-8-aldehyde and gives rise to 4-methyl-coumarino-7 : 8-α-pyrone by treatment with sodium acetate and acetic anhydride.

By the condensation of malic acid with umbelliferon in the presence of sulphuric acid a product (A) is obtained melting at about 246° C. (not sharp) as recorded by Sen and Chakravarti. It resembles coumarino-7 : 8-α-pyrone very closely in properties. But the latter melts about 12° higher (258–60° C.) and the mixed melting point was in between. On closely examining (A), however, it was realised that it was a mixture of two substances which could be separated by virtue of the marked difference in solubility between them. The more easily soluble fraction was the major portion (95 per cent.) and was found to be identical with coumarino-7 : 8-α-pyrone in all respects. The less easily soluble fraction melted at a much higher temperature (334–35° C.). It is isomeric with the major product and is obviously the linear coumarino-7 : 6-α-pyrone. This is in agreement with the general observation that linear isomers are more sparingly soluble and melt at a higher temperature than the corresponding angular ones. [Compare psoralen and isopsoralen

(angelicin).[5]] The conclusion could therefore be drawn that when two alternatives are available the predominant tendency is to form the angular compound. However, the formation of the linear variety is also possible, though to a small extent.

The product obtained from 4-methylumbelliferon and malic acid was found to resemble 4-methylcoumarino-7 : 8-α-pyrone in all properties ; the melting points were identical and the mixed melting point undepressed. It seemed to be a single compound and no isomer could be isolated as in the previous case, in spite of repeated attempts at fractionation.

The condensations of umbelliferon and 4-methylumbelliferon with ethylacetoacetate have also been examined. Umbelliferon did not undergo any condensation with either sulphuric acid or alcoholic hydrogen chloride. In the presence of sulphuric acid 4-methylumbelliferon and ethylacetoacetate give only a poor yield of the product which can be obtained in better quantities by the action of alcoholic hydrogen chloride on resorcinol and ethylacetoacetate. The substance has a sharp melting point which does not change by repeated recrystallisations, and it could not be separated into two compounds by fractional crystallisation. It is, therefore, described as 4 : 4′-dimethylcoumarino-7 : 8-α-pyrone.

Experimental.

7-Hydroxycoumarin-8-aldehyde[4] was prepared according to the directions given by Späth. The smallness of the yield was found to be due to the production of a large amount of a complex, sparingly soluble, yellow by-product. When large quantities of umbelliferon were employed (Späth, 20 gm.) the by-product used to be obtained in disproportionately high yield, and the yield of the aldehyde was unsteady and poor. With smaller quantities, about 5 gm., the yield was consistently about 0·6 gm.

Coumarino-7 : 8-α-pyrone.—The above aldehyde (0·5 g.) was heated with fused sodium acetate (1 g.) and acetic anhydride (10 c.c.) for 7 hours in an oil-bath kept at 180° C. The product was poured into cold water (300 c.c.) and the solid that separated on leaving overnight was filtered and recrystallised first from glacial acetic acid and then from pyridin. It came out as rhombic plates and needles melting at 258–60°C., to a brown liquid. The yield was 0·5 g. [Found : C, 67·1 % ; H, 3·1 % ; $C_{12}H_6O_4$ requires C, 67·3 % ; H, 2·8 %.]

The substance is sparingly soluble in ether, alcohol and benzene and dissolves fairly easily in acetic acid and pyridin. It is unaffected by aqueous sodium carbonate and dissolves only very slowly in aqueous ammonia and sodium hydroxide in the cold and more rapidly on heating.

Condensation of malic acid with umbelliferon.—This condensation was effected according to the method of Sen and Chakravarti[3] and a fairly good yield of a colourless crystalline product (55%) was obtained. It was noticed that if hot ammonia should be employed for removing unchanged umbelliferon, considerable loss of the coumarinopyrone was sustained and that maceration with cold dilute ammonia was sufficient. The product was once crystallised from glacial acetic acid. It was quite crystalline and almost colourless. But the melting point was not sharp, the mass sintering from 242° C. and melting down completely at about 248° C. (Sen and Chakravarti, 245–50° C.). Ordinary methods of crystallisation did not raise the melting point appreciably.

Separation of the mixture.—By boiling the product with an insufficient quantity of acetic acid or pyridin and filtering hot a small amount of a sparingly soluble fraction was left behind on the filter. This was kept separately. The solution now deposited a colourless crystalline solid which melted at about 255° C. On further crystallisation from pyridin it gave rhombic plates and needles melting at 258–60° C., and was found to be identical with coumarino-7 : 8-α-pyrone obtained from 7-hydroxycoumarin-8-aldehyde. A mixed melting point showed no depression. [Found : C, 67·3 % ; H, 3·0 % ; $C_{12}H_6O_4$ requires C, 67·3 % ; H, 2·8 %.]

Isolation of coumarino-7 : 6-α-pyrone.—The sparingly soluble fraction on the filter melted above 300° C. It was markedly less soluble than the other product in all organic solvents. It could however be crystallised from boiling pyridin as colourless rectangular tablets and prisms. The substance has a tendency to come out invariably in hard big crystals. It melts at 334–35° C. with sintering at about 330° C. and then decomposes. In its reaction towards alkali it resembles coumarino-7 : 8-α-pyrone. [Found : C, 67·2 % ; H, 3·0 % ; $C_{12}H_6O_4$ requires C, 67·3 % ; H, 2·8 %.] The yield of this compound was about 5% of the crude mixture obtained from the condensation, the rest being the 7 : 8 isomer.

4-Methyl-7-hydroxycoumarin-8-aldehyde.—This was prepared from 4-methylumbelliferon by the same method as was employed with umbelliferon. The substance was obtained as colourless thick plates on evaporating the final ether extract. When recrystallised from aqueous alcohol it melted at 176° and the yield was found to be 0·6 g. from 4·5 g. of the starting material. [Found : C, 64·3% ; H, 4·0 % ; $C_{11}H_8O_4$ requires C, 64·7 % ; H, 3·9 %.] The substance was easily soluble in the ordinary solvents like ether and alcohol. An aqueous solution gave an intense violet colour with ferric chloride. It formed a phenyl-hydrazone which crystallised out from alcohol

as long fine needles melting at 251–52° C., and a semicarbazone crystallising as needles and narrow plates which does not melt below 300° C. but changes colour on heating—colourless at the ordinary temperature, turning yellow at about 180° C. and greenish blue at about 300° C.

Reduction to 4 : 8-*dimethyl-7-hydroxycoumarin.*—The above aldehyde was dissolved in glacial acetic acid, treated with palladium charcoal (prepared from animal charcoal and palladium chloride) and shaken in an atmosphere of hydrogen till 2 molecular proportions of the gas were absorbed.[6] The solution was then filtered and the solvent removed by distillation under reduced pressure. The residue was then treated with water, the remaining acid just neutralised with sodium carbonate and the reduction product removed by extraction with ether. The ether solution was then shaken with a saturated solution of sodium bisulphite to remove any unreduced aldehyde and washed with water. Evaporation of the solvent gave 4 : 8-dimethylumbelliferon which on recrystallisation from alcohol appeared as rectangular plates and tablets, melting at 257–58° C. [Found : C, 69·5 % ; H, 5·4 % ; $C_{11}H_{10}O_3$ requires C, 69·5 % ; H, 5·3 %.] A mixture of this with the specimen made from 2-methylresorcinol (see below) melted at the same temperature.

Preparation of 4 : 8-*dimethyl-7-hydroxycoumarin from* 2-*methylresorcinol.*—2-methylresorcinol was prepared from β-resorcylic acid by following the method adopted by Robinson and Shah[7] for 2-ethylresorcinol. The acid was smoothly converted into the methyl ester by boiling with anhydrous methyl alcohol containing 5–6% hydrogen chloride or concentrated sulphuric acid for about 4 hours. It was then methylated using methyl iodide (5 mols.) and methyl alcoholic potash (4 mols.). The resulting product was macerated with cold dilute sodium hydroxide. The portion insoluble in alkali was found to be methyl 3-methyl-4-methoxy-β-resorcylate. It crystallised from methyl alcohol as rectangular tablets, melting at 76–77° C. By direct treatment with concentrated hydriodic acid this ester gave 2-methylresorcinol by simultaneous hydrolysis, decarboxylation and demethylation. But the yield and purity were not satisfactory. Therefore, the ester was hydrolysed with alcoholic potash just as the previous workers have done and the resulting acid subjected to the action of hydriodic acid.[7,8] 2-Methylresorcinol was easily obtained pure on recrystallisation from benzene—light petroleum mixture from which it was deposited as elongated prisms, melting at 115–16° C. It gave the fluorescein reaction with phthalic anhydride.

A mixture of equimolecular proportions of 2-methylresorcinol and ethyl-acetoacetate was treated with twice the weight of concentrated sulphuric

acid and allowed to stand overnight at the laboratory temperature. 4 : 8-dimethyl-7-hydroxycoumarin was isolated by pouring the mixture into water, filtering and washing with water. It crystallised from alcohol as thin rectangular plates, melting at 257–58° C. [Found : C, 69·5 % ; H, 5·2 % ; $C_{11}H_{10}O_3$ requires C, 69·5% ; H, 5·3%] and was found to be identical with the sample obtained above by the reduction of 4-methyl-7-hydroxycoumarin-8-aldehyde.

4-*Methylcoumarino*-7 : 8-α-*pyrone*.—4-Methyl-7-hydroxycoumarin-8-aldehyde was treated with sodium acetate and acetic anhydride for 7 hours at 180° C. and the product isolated as usual. It crystallised from glacial acetic acid as colourless fine needles, melting at 304–5° C. to a brown liquid. [Found: C, 67·8 % ; H, 3·9 % ; $C_{13}H_8O_4$ requires C, 68·4 % ; H, 3·5 %.]

Condensation of malic acid with 4-*methyl*-7-*hydroxycoumarin*.—The mixture of the two was treated with concentrated sulphuric acid and heated at 100° C. for 4 hours (Sen and Chakravarti[3]). The solid obtained on pouring it into water was digested with cold dilute ammonia to remove any unchanged hydroxycoumarin and recrystallised from glacial acetic acid. In every respect it was identical with 4-methylcoumarino-7 : 8-α-pyrone. The melting point of the mixture was undepressed. A close examination of the crude product by the method of fractional crystallisation did not reveal any heterogeneity.

4 : 4′-*Dimethylcoumarino*-7 : 8-α-*pyrone*.—The following methods were examined. Since only one substance could be obtained as the product it could be taken to be 4 : 4′-dimethylcoumarino-7 : 8-α-pyrone—m.p. 333–5° C. All properties agree with the description given by Sen and Chakravarti.

Resorcinol (1 mol.) condensed with ethylacetoacetate (2 mols.) to produce an insignificant yield of the coumarinopyrone when cold sulphuric acid was used and 20 per cent. yield when alcoholic hydrogen chloride was used as the condensing agent. With the latter condensing agent the yield was 5–6 per cent. when only one molecule of ethylacetoacetate was employed. With 4-methylumbelliferone (1 mol.) and ethylacetoacetate (1 mol.) the yield of the coumarinopyrone was negligible in the presence of alcoholic hydrogen chloride and 10–15 per cent. with sulphuric acid.

Summary.

When umbelliferon condenses with malic acid two isomeric compounds are formed. The angular coumarino-7 : 8-α-pyrone is the major product (95%) and its constitution is established from its preparation from umbelliferon-8-aldehyde by the Perkin's reaction. The second compound which should be the linear coumarino-7 : 6-α-pyrone is formed in a very small yield only (5%). Under the same conditions 4-methylumbelliferon produces

only one compound whose constitution as 4-methylcoumarino-7 : 8-α-pyrone is arrived at from its independent synthesis from 4-methylumbelliferon-8-aldehyde. The constitution of this aldehyde is deduced not only from analogy but also from its reduction to 4 : 8-dimethyl-7-hydroxycoumarin which has been prepared from 2-methylresorcinol and ethylacetoacetate. 4-Methylumbelliferon and ethylacetoacetate also give only one compound which is given the constitution 4 : 4′-dimethylcoumarino-7 : 8-α-pyrone. This compound has been found to be produced in good yield from resorcinol and ethylacetoacetate in the presence of alcoholic hydrogen chloride.

It is concluded that the angular isomer is the one invariably and most predominantly formed though the formation of the linear variety is not altogether precluded.

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