GEOMETRICAL INVERSION IN THE ACIDS DERIVED FROM THE COUMARINS.

Part IV. The Behaviour of the Ethers of the *Cis* and *Trans* Acids.

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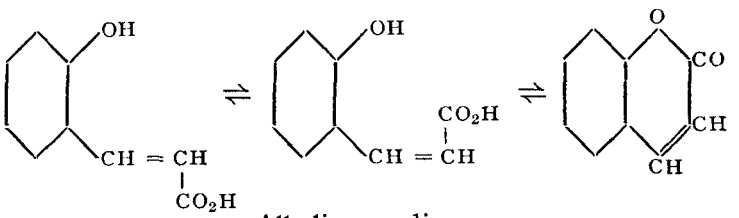
In the previous communications of this series[1,2,3] it has been shown that in the acids derived from the coumarins the change *cis* to *trans* takes place in an alkaline medium only, whereas in neutral or acid medium the tendency is to produce the reverse change. Since normally the *trans* is the stabler form, it was surmised that the abnormal depletion of the *trans* acid is due to the ready conversion of the *cis* form, which may exist in a small proportion, into the coumarin, thereby shifting the equilibrium in the direction of the *cis*. It was only when the formation of coumarin is prevented by the presence of alkali that normal conditions prevail and the *trans* acid is obtained in good yield.

Neutral or acid medium



Alkaline medium

It should be remembered that the presence of an additive reagent is necessary ordinarily, except when light energy or high temperature is made to operate.

It was therefore desirable to study the behaviour of the methyl ethers of the *cis* and *trans* acids, since in them the formation of the pyrone ring should be very difficult. The methyl ethers of the acids from coumarin, 7-methyl-coumarin and 6-nitrocoumarin have been obtained by improved methods and their transformation in neutral, acid and alkaline media studied.

It has been found that irrespective of the nature of the medium the *trans* form is the one favoured. (See the tables below.) If however the conditions facilitate the hydrolysis of the methyl ether group, as when the ethers are heated with concentrated sulphuric acid, coumarin formation takes place.

TABLE I.

Action of Mercuric Compounds.

Methyl ether of	Mercuric chloride in neutral medium	Mercuric acetate in neutral or faintly acid medium	HgO in alkaline medium
1. Coumarinic acid	Complete conversion from *cis* to *trans*	Complete conversion from *cis* to *trans*	Unaffected
2. 4-methyl coumarinic acid	do.	do.	do.
3. 5-nitrocoumarinic acid	Unaffected	Unaffected	Complete conversion from *cis* to *trans* and hydrolysis

TABLE II.

Action of Alcoholic Hydrogen Chloride and Concentrated Sulphuric Acid.

Methyl ether of	Alcoholic HCl product	H_2SO_4 product
Cis acids—		
1. coumarinic acid	*Trans* acid mostly as ester and no coumarin	14% coumarin, 5% *trans* acid and the rest lost
2. 4-methylcoumarinic acid	do.	6% coumarin, 3% *trans* acid and the rest lost
3. 5-nitrocoumarinic acid	do.	70% coumarin, 12% *trans* acid. Rest lost
Trans acids—		
1. coumaric acid	About 80% *trans* ester and rest *trans* acid. No coumarin	2% coumarin, 4% original *trans* acid ether. Rest lost
2. 4-methylcoumaric acid	About 75% *trans* ester and rest *trans* acid. No coumarin	2% coumarin, 3% original *trans* acid ether. Rest lost.
3. 5-nitrocoumaric acid	Completely *trans* ester	5% coumarin, 80% original *trans* acid ether.

The methyl ethers of coumarinic and 4-methylcoumarinic acids undergo inversion easily in neutral and faintly acid media, and their unexpected

failure to do so in the presence of alkali and mercuric oxide may be considered as partly due to the diminished capacity of the mercury compound to attack the double bond under this condition. The inversion of the nitrocoumarinic acid methyl ether in the presence of alkali is accompanied by the demethylation of the ether group. Whether this demethylation is a necessary preliminary is difficult to decide definitely ; but since in neutral medium the compound remains unchanged it may be presumed that in the alkali reaction this factor should have helped the change. Past work has clearly shown that the *cis* hydroxy acids undergo inversion to the *trans* easily in alkaline medium. If the suggestion originally made[4] that amongst the factors determining the facility of geometrical inversion in alkaline solution is to be counted the repulsion between the negative charges of the phenate and carboxylate ions is accepted, we have a rational explanation of the facts recorded above. This driving force does not exist in the methyl ethers and hence the difference in behaviour between the *cis* hydroxy acids and their methyl ethers in alkaline solution.

In the presence of alcoholic hydrogen chloride the ethers of the *cis* acids undergo inversion into the *trans* compounds and at the same time get esterified to a great extent. The *trans* acid ethers under the same conditions remain unchanged except for the esterification of the carboxyl group.

Concentrated sulphuric acid at 100° introduces a different type of conditions mainly due to its capacity as a demethylating and sulphonating agent. This explains the formation of coumarins from the methyl ethers and the considerable loss of material by the formation of soluble sulphonic acids. The *cis* acid ethers give both the *trans* acid ethers and the corresponding coumarins. The inversion to the *trans* compounds may be considered to be the normal change whereas the formation of coumarins is due to demethylation. In the case of the ether of the nitro-acid chances of demethylation are greater and sulphonation far less and hence such a large formation of the nitrocoumarin and so little loss.

Experimental.

Preparation of the required methyl ethers.

Methyl ether of coumarinic acid.—Attempts to prepare it by methylating with dimethyl sulphate a solution of coumarin in aqueous sodium hydroxide were without success, coumarin being recovered unchanged. It was however easily obtained by the method of Perkin[5] (see also Simonis[6]) in which a methyl alcoholic solution of coumarin is treated with sodium methylate and methyl iodide. It crystallised out of alcohol as glistening monoclinic crystals, melting at 91–92°.

Methyl ether of coumaric acid.—It was noticed that the method detailed in Simonis's book, *Die cumarine*, p. 87 (see also Reychler[7]) failed to give satisfactory results since mostly the ether of the *cis* acid was obtained. If however it is modified by heating the mixture of coumarin and sodium methoxide in dry alcohol for about 4 hours under reflux before treating with methyl iodide, a good yield of the ether of the *trans* acid is obtained. The preparation is markedly influenced by the presence of moisture in the alcohol.

This ether was readily obtained by methylating coumaric acid with dimethyl sulphate in the presence of sodium hydroxide. Coumaric acid was dissolved in excess of aqueous alkali and shaken with two equivalents of dimethyl sulphate for half an hour (gradual addition). It was finally heated on the water-bath for 1 hour and the ether percipitated with acid. It recrystallised from dilute alcohol as colourless narrow plates and prisms melting at 185–86°.

4-*Methyl coumarinic acid methyl ether* was obtained from 7-methyl coumarin by following the same procedure as for the ether of coumarinic acid. When crystallised from alcohol it came out as colourless stout rhombic prisms melting at 160–61°. [Found : C, 68·4%; H, 5·9%; $C_{11}H_{12}O_3$ requires C, 68·7%; H, 6·3%. Found in the silver salt : Ag, 35·9%; $C_{11}H_{11}O_3Ag$ requires Ag 36·1%.]

4-*Methyl coumaric acid methyl ether.*—4-methyl coumaric acid was obtained from 7-methyl coumarin by the method of Seshadri and Suryaprakasarao[2] and was methylated by means of dimethyl sulphate and sodium hydroxide as detailed in the case of coumaric acid methyl ether. It crystallised from aqueous alcohol as long narrow rectangular plates melting at 209–10°. [Found : C 68·3%; H, 6·0%; $C_{11}H_{12}O_3$ requires C, 68·7%; H, 6·3%. Found in the silver salt : Ag, 36·6%; $C_{11}H_{11}O_3Ag$ requires Ag, 36·1%.]

5-*Nitrocoumarinic acid methyl ether.*—Direct methylation of 6-nitrocoumarin in alkaline solution with dimethyl sulphate could not be effected. The compound was therefore obtained from 6-nitrocoumarin by following the procedure of Clayton.[8] The nitro-coumarin was converted into the di-silver salt of the coumarinic acid, from which the ether ester was made by the action of methyl iodide, and this on hydrolysis gave the required compound crystallising from alcohol as colourless needles melting at 202–3° C. It was noticed that Clayton's method of hydrolysis using boiling alcoholic sodium hydroxide gave rise to an impure product (probably due to demethylation) and considerable loss of material was sustained during the purification. The best procedure was to effect the hydrolysis with 5% aqueous potash, kept

boiling till a clear solution was obtained (5 minutes), cooling the solution and acidifying. The yield was almost quantitative and the product was readily obtained very pure by a simple crystallisation from alcohol, m.p. 202–3°.

5-*Nitrocoumaric acid methyl ether.*—(i) Direct methylation of 5-nitrocoumaric acid was not successful.

(ii *a*). 5-Nitrocoumaric acid[2] was converted into the di-silver salt as given below and this made to react with methyl iodide in ether solution. By this method was obtained the methyl ether of methyl 5-nitrocoumarate which was found to have the properties described by Clayton[8] for the compound which he obtained from 5-nitrocoumaric acid methyl ether through the silver salt.

5-Nitrocoumaric acid (21 g.) was dissolved in sodium hydroxide (8 g.) and treated with silver nitrate (35 g.) dissolved in water. The reddish silver salt was filtered, washed and dried on a porous tile in vacuum.

The dry silver salt (16 g.) was shaken with methyl iodide (16 g.) and ether (100 c.c.) for two hours. The residue left after evaporating off the ether, was then extracted with hot alcohol and the solution allowed to crystallise. The ether ester was obtained as colourless needles, m.p. 163° in a yield of about 70%.

(ii *b*). Methyl 5-nitrocoumarate[1] was methylated with methyl iodide and potassium carbonate in acetone solution.

Methyl 5-nitrocoumarate (5 g.) was dissolved in acetone (150 c.c.), dried over potassium carbonate and gently boiled with excess of methyl iodide (5 c.c.) and anhydrous potassium carbonate (10 g.) for 4 hours. Most of the acetone was then distilled off and the residue treated with water and acidified. The solid that separated was filtered, washed and recrystallised from alcohol, m.p. 163°. The yield was about 80%.

The *trans* ether ester was hydrolysed with hot 5% aqueous potash as in the case of the *cis* compound. (Stronger alkali and prolonged heating resulted in the hydrolysis of the ether group also. Both cold and hot alcoholic potash were unsatisfactory.) The product was obtained very pure by one crystallisation from alcohol, m.p. 236° and the yield was almost theoretical.

Action of mercury compounds on the ethers of the cis *acids. Mercuric oxide (alkaline medium).*—Solutions of the *cis* acid ethers in excess of aqueous potash were shaken with yellow mercuric oxide for about half an hour, filtered and the product precipitated with hydrochloric acid and examined. If cold treatment was ineffective the solution was boiled for 3 to 5 hours, filtered

and the products examined. If there should have been any mercuration the mercury was removed with hydrogen sulphide in an alkaline solution.

Coumarinic acid methyl ether and 4-methyl coumarinic acid methyl ether were unaffected by treatment in the cold. On boiling however mercurated products were produced which gave the original *cis* compounds on decomposition with hydrogen sulphide. No inversion seemed, therefore, to take place in these cases. 5-nitrocoumarinic acid methyl ether underwent complete isomerisation into the *trans* form without any mercuration, on boiling with mercuric oxide and aqueous alkali ; but at the same time it got demethylated with the result that the final product was an impure mixture. Prolonged boiling, however, gave pure 5-nitrocoumaric acid.

Mercuric Chloride (neutral medium).

The ether of the *cis* acid (1 g.) and mercuric chloride (2 g.) were dissolved in sufficient quantity of 50% aqueous alcohol and boiled for 2 to 3 hours at the end of which enough hydrochloric acid was added to make the strength 1% and allowed to cool. If no change was effected by this treatment, a simple aqueous solution of mercuric chloride was used and the boiling continued for 6 hours.

The methyl ethers of coumarinic and 4-methyl-coumarinic acids were easily converted into the *trans* ethers in good yield, whereas the ether of 5-nitrocoumarinic acid was unaffected in aqueous-alcoholic or aqueous medium.

Mercuric acetate (neutral or weak acid medium).

The ether of the *cis* acid was dissolved in aqueous sodium hydroxide, neutralised with acetic acid and then treated with an aqueous solution of mercuric acetate slowly with stirring. The bulky precipitate that was produced was filtered off after an hour, dissolved in aqueous caustic soda and saturated with hydrogen sulphide. After filtering off mercuric sulphide, the filtrate was acidified and the product examined after crystallisation from alcohol, if necessary.

The ethers of coumarinic and 4-methyl-coumarinic acids gave good yields of the *trans* isomers, whereas the ether of 5-nitrocoumarinic acid was unaffected. This nitro acid was also treated with boiling methyl alcoholic mercuric acetate. The reaction was very slow and the product did not yield the pure *trans* acid though it had undergone some change.

Action of alcoholic hydrogen chloride on the ethers of the cis *acids.*

The ether was dissolved in sufficient quantity of anhydrous alcohol, saturated with dry hydrogen chloride at 0° and allowed to stand for 24 hours

at room temperature. It was then refluxed for 2 hours, most of the alcohol distilled off, the residue treated with water and ether-extracted. The ether solution was then shaken with small volumes of aqueous sodium carbonate in order to remove the acid portion and then washed with a small volume of water. After drying over anhydrous calcium chloride it was evaporated in a tared flask and the neutral residue weighed and examined. The carbonate solution was acidified, ether-extracted and the acid portion obtained and examined separately.

The ether of coumarinic acid was completely converted into the *trans* form and most of it (about 80%) esterified. On hydrolysing the neutral portion pure ether of the *trans* acid was obtained in good yield and no coumarin could be detected. The acid portion was pure *trans* acid ether (10–15%).

The methyl ether of 4-methyl-coumarinic acid gave rise to a complex neutral product with dry alcohol saturated with hydrogen chloride. It contained however no coumarin. On hydrolysis it gave rise to an acid which could not be obtained pure. On using however aqueous alcohol (1 : 1) containing hydrochloric acid (3 c.c. of concentrated acid in 40 c.c. of the mixture) it smoothly underwent inversion giving mostly the ester of the *trans* acid ether.

The ether of 5-nitrocoumarinic acid was almost completely esterified and simultaneously transformed into the *trans* form. Methyl ether of ethyl 5-nitro-coumarate, m.p. 85° (Clayton[8]) was obtained (80–85%) and yielded on hydrolysis the ether of the *trans* acid. No coumarin could be detected.

Action of alcoholic hydrogen chloride on the ethers of the trans *acids.*—

The same procedure as with the *cis* ether was adopted. The ether of coumaric acid underwent conversion into the ester to about 80%. No further change could be noted and no coumarin was formed.

In the case of the ether of 4-methyl-coumaric acid, 25% of the acid was recovered unchanged and the rest was found to be an ester free from 7-methyl coumarin. But on hydrolysing the ester, the acid that was obtained could not be purified or characterised. It seemed to have undergone some complex changes. This did not happen if aqueous-alcoholic hydrochloric acid was employed. The *trans* acid ether was unchanged except for partial esterification.

The methyl ether of 5-nitro-coumaric acid with methyl alcohol as the solvent was converted almost completely into a neutral compound melting at 162° and found to be identical with the methyl ester of the original *trans* acid.

Action of concentrated sulphuric acid.

On the cis *ethers.*—The compound (1 g.) was treated with concentrated sulphuric acid (10 c.c.) and heated at 100° for one hour. It was then cooled, poured into cold water (100 c.c.) and the product worked up in the same way as was adopted with alcoholic hydrogen chloride.

The methyl ether of coumarinic acid gave 14% coumarin; about 5% of the corresponding *trans* acid could be isolated and the rest was lost by sulphonation. From the ether of 4-methylcoumarinic acid only 6% yield of 7-methyl-coumarin could be obtained, along with 3% of the ether of the *trans* acid; the rest was lost. The ether of 5-nitrocoumarinic acid gave about 70% of 6-nitrocoumarin and about 12% of the *trans* acid ether; the rest was lost.

On the trans *ethers.*—The same procedure as described above was adopted. The methyl ethers of coumaric and 4-methyl-coumaric acids gave about 2% yield of the corresponding coumarins. Only 3 to 5% of the unchanged acids were recovered and the rest was lost. From the ether of 5-nitro-coumaric acid was obtained about 5% yield of 6-nitrocoumarin and about 80% of the original *trans* acid ether was recovered unchanged.

Summary.

The methyl ethers of the *cis* and *trans* acids from coumarin, 7-methyl-coumarin and 6-nitrocoumarin have been obtained by improved methods and their transformation in neutral, acid and alkaline media studied. It has been found that irrespective of the nature of the medium the *trans* form is the one favoured, thereby showing that the unusual depletion of the *trans* hydroxy acids (coumaric acids) in neutral and acid media is due to the ready formation of coumarins from the corresponding *cis* acids, which may exist in small proportions in equilibrium with the *trans*. This ring closure is prevented in the methyl ethers. If however conditions favour the hydrolysis of the ether group as when the compounds are heated with concentrated sulphuric acid coumarin formation takes place to some extent.

REFERENCES.

1. Dey, Rao and Seshadri, *J.I.C.S.*, 1934, **11**, 743.
2. Seshadri and Suryaprakasarao, *Proc. Ind. Acad. Sci.*, (A), **3**, 293.
3. „ „ **4**, 157.
4. Seshadri, *Curr. Sci.*, **3**, 19-20.
5. Perkin, *J.C.S.*, 1881, **39**, 409.
6. Simonis, *Die cumarine, Verlag von Ferdin and Enke*, p. 86.
7. Reychler, *Bull. Soc. Chem.*, **3**, 553.
8. Clayton, *J.C.S.*, 1910, **97**, 2102.