GEOMETRICAL INVERSION IN THE ACIDS DERIVED FROM THE COUMARINS.

Part V. The Behaviour of Psoralic and Isopsoralic Acids.

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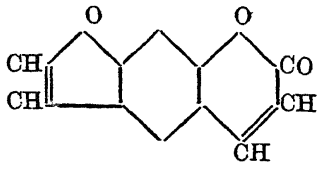
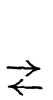
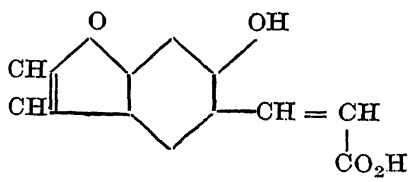
The early attempts of Karrer, Glattfelder and Widmer[1] to prepare members of the Bergapten group starting from hydroxycoumarones ended in failure. As a possible explanation for this it was suggested (Ray *et al.*[2]) that the intermediate hydroxycoumarone acrylic acids produced in their experiments had the *trans*-configuration and hence did not undergo ring closure. This led us to examine some *trans* acids of this series with reference to their capacity to undergo geometrical inversion and ring closure. Two of this group can be easily made from Psoralen (I) and Isopsoralen (II) which have been recently obtained from the seeds of *Psoralia Corylifolia*.[3,4,5] The *cis* acids from these two substances are unstable and are formed only in alkaline solutions. They are now named Psoralinic and Isopsoralinic acids. Their methyl ethers are, however, stable and have been prepared by Jois and Manjunath[4] by methylating the alkaline solutions. The stable *trans* acids have not hitherto been made, though their ethers were obtained by the above authors by the sublimation of the *cis* acid ethers *in vacuo*. These *trans* acids have now been obtained by the method of Seshadri and Rao using cold mercuric oxide and caustic soda.[6] They are named Psoralic (III) and Isopsoralic acids (IV). They are stable and they confirm to the behaviour of stable *trans* acids in all their reactions. They have been converted into their methyl ethers which were originally obtained from the *cis* compounds by sublimation *in vacuo*.[4]



Psoralen (coumarono-6 : 5-α-pyrone).

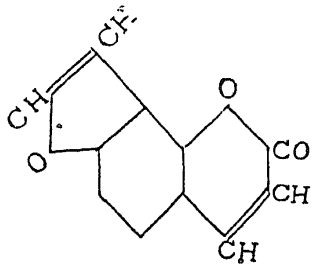
I





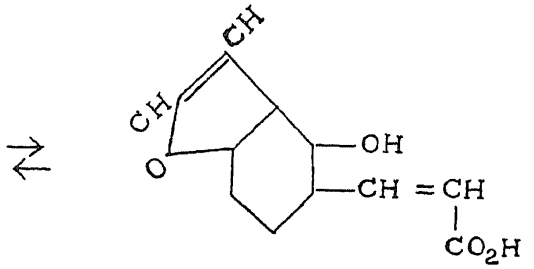
Psoralic acid (6-hydroxycoumarone-5-acrylic acid).

III



Isopsoralen (coumarono-4 : 5-α-pyrone).

II



Isopsoralic acid (4-hydroxycoumarone-5-acrylic acid).

IV

Psoralic and Isopsoralic acids are isomeric and offer scope for studying the influence of structure on the facility with which ring closure to the pyrone can take place. As will be noticed the first acid will give rise to a linear and the second to an angular compound and in general it is known that the formation of an angular ring compound is favoured (see Rangaswami and Seshadri[7]). In the ring formation from the above two acids there are two factors that are involved : (1) the facility with which *trans* to *cis* inversion takes place and (2) the ease with which ring closure with the elimination of water takes place.

In the presence of concentrated sulphuric acid the above hydroxy-coumarone-acrylic acids were unstable and were rapidly converted into dark resinous products from which no crystalline substance could be isolated. On the other hand they underwent smooth conversion into the corresponding coumarono-α-pyrones in the presence of sunlight. By comparative experiments it was found that the change was more ready in the case of Isopsoralic acid (75 per cent. in 16 hours) than with Psoralic acid (58 per cent.). When aqueous mercuric chloride was employed there was some resinification so that no comparisons could be correctly made though in this case also Isopsoralic acid gave a better yield of the pyrone (50 per cent.) than Psoralic acid (25 per cent.). To which of the two factors that have been mentioned in the previous paragraph this difference should be attributed is difficult to decide.

In the examples studied in this paper, though the angular compound appears to be more readily formed than the linear variety, still the difference is not great when comparison is made with the formation of fresh rings starting from only one group like the OH or NH_2. In these cases the angular compound is either the sole product or is predominantly the major product. This seems to be obviously due to the reactivity of the alternative nuclear positions one of which is preferentially favoured.

Experimental.

The best method of isolating the crude mixture of Psoralen and Isopsoralen from the seeds of *Psoralia Corylifolia* has already been discribed.[5] It melted at about 110°–115°. The separation of the two was

effected as follows :—5 grams of the mixture was dissolved in a fair excess of boiling ethyl alcohol, filtered from any suspended impurities and allowed to cool slowly. Colourless, large and hard crystals (rhombohedral plates and prisms) were obtained in the course of two hours. The mixture was then stirred, filtered and the crystals washed with a small quantity of alcohol. The solid now melted at 156°–58° with a little previous sintering. A further crystallisation from aqueous alcohol raised the melting point to 167°–68° (Jois *et al.* 162° ; Spath *et al.* 171°). This had all the properties of Psoralen as described by Jois *et al.*[3] (yield 2·2 g.).

The alcoholic mother liquor on concentration to half its bulk and cooling gave a crop of soft fine needles melting at 128°–32°. Two further crystallisations from dilute alcohol raised the melting point to 141°–42° (Jois and Manjunath[4] gave for Isopsoralen 142° and Spath and Pesta gave for Angelicin 139°).[8] This compound agreed with previous descriptions of Isopsoralen and Angelicin (yield 0·8 g.).

The residual alcoholic mother liquor on further concentration and treatment with water gave a large crop of a crystalline solid melting at 118°–20°. Repeated crystallisation from alcohol did not produce any change and the melting point was fairly sharp. Analysis however, showed that it had the same composition as Psoralen or Isopsoralen and was obviously a mixture of the two having the characteristic of a fairly sharp melting point [Found : C, 70·9, H 3·4 ; $C_{11}H_6O_3$ requires C, 71·0, H, 3·2%]. It was therefore dissolved in chloroform in which it was readily soluble and treated with ether till precipitation just occurred. The precipitated solid was collected after twelve hours and was found to be mostly Psoralen which could now be rendered pure by two crystallisations from dilute alcohol. The chloroform ether solution gave a solid on evaporation from which small quantities of Isopsoralen could be isolated by repeated crystallisation from aqueous alcohol. Fractional crystallisations using carbon tetrachloride or pyridine were also found to be effective. Psoralen was comparatively easily obtained from the more sparingly soluble portions whereas the separation of Isopsoralen was far more difficult and tedious.

Preparation of Psoralic acid.—Psoralen (1 g.) was dissolved in hot 5% aqueous sodium hydroxide (20 c.c.), the solution cooled to room temperature, treated with yellow mercuric oxide (0·5 g.) and shaken vigorously for about 15 minutes. The mixture was then filtered through an ordinary filter and the residue washed with a little water. The filtrate was then saturated with hydrogen sulphide and after mercury had been completely precipitated, it was filtered and washed with small quantities of water. On strongly acidifying the filtrate Psoralic acid was obtained, as a crystalline

solid melting at about 220° with decomposition. It was easily crystallised from aqueous alcohol as rectangular prisms melting with decomposition at 225°–27° [Found : C, 64·2 ; H, 4·0 ; $C_{11}H_8O_4$ requires C, 64·7 ; H, 3·9%]. It was noticed that during the shaking with mercuric oxide considerable mercuration occurred. If the combined mercury was not removed as described above the precipitated acid melted at about 195°. The yield under the best conditions was 90%. Care had to be taken that no rise of temperature was allowed to take place during the course of the preparation and during acidification. Cooling with ice was employed.

Methyl ether of Psoralic acid.—Psoralic acid (0·4 g.) was dissolved in a mixture of methyl alcohol (6 c.c.) and 20% sodium hydroxide (10 c.c.). After raising the temperature to 80°, the solution was agitated vigorously and methyl sulphate (2 c.c.) was added. The mixture turned milky on shaking. It was then heated on a water-bath at 80° for 5 minutes, treated with 6 c.c. more of the alkali and heated for 5 minutes more with vigorous agitation. Methyl sulphate (2 c.c.) and alkali (6 c.c.) were now added alternately with shaking and heating between the additions till the methyl sulphate introduced amounted to 8 c.c. Finally 6 c.c. of methyl sulphate and 12 c.c. of alkali were added and the mixture refluxed on a steam-bath for 30 minutes longer. The contents were cooled, filtered and acidified. The crude methyl ether was obtained in a yield of 90%. It is easily soluble in alcohol, acetic acid and pyridine and was crystallised from aqueous pyridine as rhombic prisms melting at 223°–24°. Jois and Manjunath who obtained this ether by sublimation *in vacuo* of the ether of the *cis* acid give the melting point as 234°–5° [Found : C, 66·5 ; H, 4·8 ; $C_{12}H_{10}O_4$ requires C, 66·1 ; H, 4·6%].

Isopsoralic acid.—This acid was obtained from Isopsoralen by closely following the method used for Psoralic acid and a similar high yield was obtained. It came down as colourless rectangular tablets from dilute alcohol and melted at 173°–75° with decomposition [Found : C, 64·5, H, 4·2 ; $C_{11}H_8O_4$ requires C, 64·7 ; H, 3·9%].

The *Methyl ether* of Isopsoralic acid was obtained by methylation as described already. It crystallised from dilute pyridine in rhombic plates melting at 213°–14°. Jois and Manjunath gave the melting point of the sample obtained by the sublimation of the *cis* compound as 214° [Found : C, 65·6 ; H, 4·9 ; $C_{12}H_{10}O_4$ requires C, 66·1 and H, 4·6%].

Conversion of the trans *acids into the pyrones.*—(i) In the presence of concentrated sulphuric acid the acids underwent complex decomposition and were rapidly converted into dark resinous products from which no definite compound could be isolated.

(ii) *Exposure to sunlight.*—The acid (about 1 g.) was weighed correctly and dissolved in anhydrous ethyl alcohol (50 c.c.) contained in a quartz round bottom flask of capacity 100 c.c. The solution was then exposed to direct sunlight for 16 hours (2 days of 8 hours—8 A.M. to 4 P.M.). The solvent was distilled off and the residue taken up in a mixture of chloroform and ether. This solution was extracted with 5% aqueous sodium carbonate till no more acid was removed and the correct stage could be ascertained from the colour of the aqueous extract. Two extractions were usually found to be sufficient. The chloroform-ether was washed with a small quantity of water, dried over calcium chloride and finally distilled in a tared conical flask to remove the solvent. The residue after being dried in a vacuum desiccator was weighed. This consisted of the coumaronopyrone (furanocoumarin) as could be ascertained from its melting point. From the aqueous sodium carbonate extract the acid could be recovered by acidification and filtration. Psoralic acid gave 58% yield of Psoralen whereas Isopsoralic acid gave 75% yield of Isopsoralen.

(iii) *Boiling with aqueous mercuric chloride.*—Psoralic acid (1 g.) was treated with water (100 c.c.) and mercuric chloride (0·5 g.) and the mixture boiled for 3 hours. A good amount of an amorphous solid was formed. Concentrated hydrochloric acid (4 c.c.) was added to the hot solution and then allowed to cool slowly. The solid matter was then filtered and dissolved in a mixture of chloroform and ether. A fair amount of a complex resinous matter was left behind and no crystalline compound could be obtained from it. The chloroform-ether solution was then extracted repeatedly with aqueous sodium bicarbonate in order to remove unconverted acid, washed with water and subsequently with dilute hydrochloric acid and then evaporated in a tared flask. Pure Psoralen was then obtained in a yield of 25%.

Starting with Isopsoralic acid the conversion was carried out in the same way. There was very little of resin formation and the yield of Isopsoralen was 50%.

Summary.

The stable *trans* acids, Psoralic and Isopsoralic acids, have been prepared from Psoralen and Isopsoralen. With concentrated sulphuric acid they undergo complex changes whereas in the presence of sunlight and aqueous mercuric chloride they yield the original pyrones. Though Isopsoralic acid undergoes ring closure more easily the difference is not great.

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