

SYNTHETIC EXPERIMENTS IN THE BENZOPYRONE SERIES

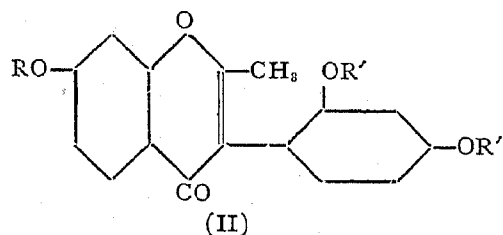
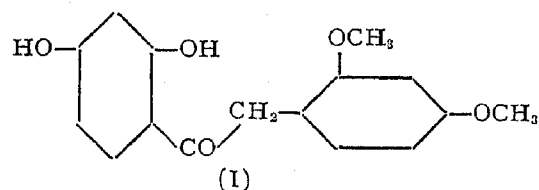
Part LV. A Synthesis of 7 : 7'-Dihydroxy Chromeno-(3' : 4' : 2 : 3)-Chromone

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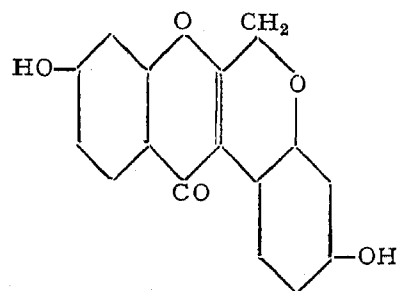
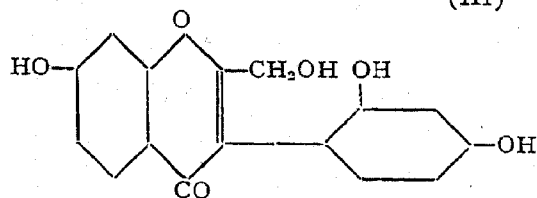
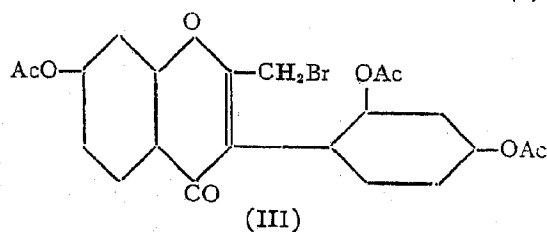
In an earlier publication¹ the considerations that led to the discovery of a new route for the synthesis of chromenochromones were discussed and a simple member of the class, *i.e.*, 7-hydroxy chromeno-(3' : 4' : 2 : 3)-chromone was prepared. In developing this method for the synthesis of more complex types ultimately leading to the synthesis of the rotenoids themselves, a higher member of the series has now been prepared, *i.e.*, 7 : 7'-dihydroxy compound (V) starting from 2 : 4-dihydroxy phenyl 2' : 4'-dimethoxy benzyl ketone (I). The various stages are represented by the following formulæ:



(a) R=Ac, R'=Me

(b) R=H, R'=Me

(c) R=R'=H



*Experimental**2:4-Dimethoxyphenyl acetonitrile*

Method I.—The following improvements were made in the method of Mitter and Maitra.²

β -Resorcyaldehyde was methylated by the dimethyl sulphate and potassium carbonate method (40 hours) giving an improved yield of the dimethyl ether. Its conversion into the azlactone is more complete if the initial refluxing with hippuric acid and acetic anhydride for an hour is followed up by further heating for two hours on a boiling water-bath. A good yield of almost pure product is obtained by adding more alcohol and leaving the mixture overnight. When recrystallised it melted at 181–82° with slight sintering at 168°. Mitter and Maitra² reported it to melt at 168°. The pyruvic acid obtained by the decomposition of the azlactone melted at 161–62°. Mitter and Maitra, 156°. Its oxime could be crystallised from methanol as colourless needles melting at 148–49° (decomp.); Mitter and Maitra, 145°.

Method II.—2:4-Dimethoxyphenyl acetic acid was prepared from resacetophenone dimethyl ether (27 g.) following the method of King and Neill³ using Willgerodt reaction. It was found advantageous to remove excess of morpholine from the crude morpholide by distillation. The acetic acid (12 g.) was converted into the acid chloride by means of thionyl chloride and treated with ice-cold liquor ammonia (50 c.c.; 0.9) gradually in the course of 15–20 minutes. The solid amide was crystallised from hot water yielding colourless broad plates, m.p. 133–34°; 10 g. It (5 g.) was mixed with phosphorus pentoxide (8 g.) and distilled under reduced pressure when the nitrile passed over between 165–70° (5 mm.); m.p. 75–6°; 2.2 g. The dehydration of the amide by refluxing with excess of acetic anhydride and sodium acetate for half an hour and subsequent treatment with ice did not give good yields.

2:4-Dihydroxyphenyl-2':4'-dimethoxy benzyl ketone (I)

To a solution of 2:4-dimethoxyphenyl acetonitrile (5 g.) and dry resorcinol (5 g.) in dry ether (150 c.c.) was added fused zinc chloride (2 g.) and the mixture saturated with dry hydrogen chloride (10 hours; 0° C.). The contents were left in an ice-chest for 24 hours when the ketimine hydrochloride first formed as a viscous liquid gradually solidified. It was separated, washed twice with small quantities of ether (20 c.c. each) and then heated with water (100 c.c.) in a boiling water-bath (6 hours). On cooling the ketone separated out. It was filtered and crystallized from dilute alcohol yielding colour-

less tiny prisms melting at 158–59°; 4.5 g. (Found: C, 66.8; H, 5.6; $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6%). It gave a reddish pink colour with alcoholic ferric chloride.

7-Acetoxy-2':4'-dimethoxy-2-methyl isoflavone (II a)

The above dihydroxy ketone (I) (3 g.) was refluxed with acetic anhydride (25 c.c.) and fused sodium acetate (6 g.) in an oil-bath for 18 hours at 170–75° and then poured over crushed ice (500 g.) and stirred for 2 hours. The acetic acid formed was neutralized by aqueous sodium bicarbonate and the mixture left overnight in the refrigerator when the isoflavone (II a) separated as a crisp solid. It was crystallized from dilute alcohol and then from benzene-light petroleum mixture yielding colourless tiny prisms, m.p. 190–91°; 2.5 g. (Found: C, 67.3; H, 4.9; $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%).

7-Hydroxy-2':4'-dimethoxy-2-methyl isoflavone (II b)

The above acetoxy compound (II a) (0.2 g.) was refluxed with boiling alcohol (10 c.c.) and concentrated hydrochloric acid (10 c.c.) for 2 hours, diluted with water (50 c.c.), and left in the refrigerator for 4 hours. The solid crystallized from ethyl acetate-petroleum ether mixture as grey coloured needles and rectangular prisms melting at 261–62°; 0.16 g. (Found: C, 68.6; H, 5.1; $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.1%). 7:2':4'-Tri-methoxy-2-methyl isoflavone obtained by the methylation of the hydroxy compound (0.15 g.) with dimethyl sulphate and potassium carbonate in acetone medium crystallized from ethyl acetate-petroleum ether mixture as short prisms melting at 192–94°. Yield 0.15 g.

7:2':4'-Trihydroxy-2-methyl isoflavone (II c)

(a) *With aluminium chloride.*—2-Methyl-7-acetoxy-2':4'-dimethoxy isoflavone (II a) (2.5 g.) was dissolved in dry benzene (100 c.c.), anhydrous aluminium chloride (7 g.) added and the mixture refluxed for 2 hours on a water-bath. The dark viscous mass left behind after removal of the solvent was treated with crushed ice (100 g.) and hydrochloric acid (25 c.c.). The mixture was boiled for 2 minutes and then cooled when the product solidified. It was dissolved in 2% cold aqueous sodium hydroxide (200 c.c.). The solution was extracted with ether and then acidified with hydrochloric acid when 7:2':4'-trihydroxy-2-methyl isoflavone (II c) precipitated out. It crystallized from ethyl acetate and acetone mixture as colourless tiny prisms melting at 254–55° (decomp.); 1.1 g. (Found: C, 64.0; H, 4.7; $C_{16}H_{12}O_5, H_2O$ requires C, 63.6; H, 4.6%). The compound did not give

any colour with alcoholic ferric chloride and also showed no fluorescence with concentrated sulphuric acid.

(b) *With hydriodic acid.*—2-Methyl-7-acetoxy-2':4'-dimethoxy isoflavone (II a) (0.5 g.) was heated with acetic anhydride (5 c.c.) and hydriodic acid (5 c.c.; d. 1.7) at 140–42° for 2 hours, then diluted with water (100 c.c.) and left in the refrigerator for 2 hours. The free iodine was removed by passing sulphur dioxide. The solid was filtered and crystallized from ethyl acetate-petroleum ether mixture; colourless prisms, m.p. 254–56° (decomp.); 0.1 g. 7:2':4'-Triacetoxy-2-methyl isoflavone obtained by acetylation of the trihydroxy compound (0.4 g.) with acetic anhydride and sodium acetate crystallized from alcohol and then from carbon tetrachloride as short thick wedge-shaped prisms melting at 178–80°; 0.38 g. (Found: C, 63.9; H, 4.8; $C_{22}H_{18}O_8$ requires C, 64.4; H, 4.4%).

7:2':4'-Triacetoxy-2-bromomethyl isoflavone (III)

A solution of the above triacetoxy isoflavone (0.62 g.), N-bromosuccinimide (0.27 g., 1 mole) and benzoyl peroxide (0.03 g.) in dry carbon tetrachloride (100 c.c.) was refluxed for 20 hours on a water-bath. The solvent was distilled off and the reddish yellow viscous mass left behind, washed with a large excess of boiling water (200 c.c., 2 lots) to remove succinimide and then treated with ice-cold water when a crisp solid was obtained. It crystallized from excess of alcohol as colourless needles melting at 201–03°; 0.45 g. (Found: C, 53.4; H, 3.7; $C_{22}H_{17}O_8Br$ requires C, 54.0; H, 3.5%).

7:7'-Dihydroxy-chromeno-(3':4':2:3)-chromone (V)

The above bromomethyl isoflavone (III) (0.4 g.) was refluxed with alcohol (20 c.c.) and hydrobromic acid (20 c.c., 40%) for 2 hours on a water-bath, diluted with water (100 c.c.) and left overnight in the refrigerator. 7:2':4'-Trihydroxy-2-hydroxymethyl isoflavone (IV) that separated was collected and dried; 0.2 g. It did not give any test for bromine. Attempts to crystallize it were not successful and hence it was used as such for the next stage. It (0.2 g.) was dissolved in dry acetone (50 c.c.), ignited potassium carbonate (5 g.) added and the mixture refluxed for 12 hours, the solvent distilled off and the residue treated with ice-water (150 c.c.), when a clear solution was obtained which on acidification yielded the chromeno-chromone (V). It crystallized from alcohol as short prisms, m.p., 280–82° (sinters at 266°) 0.08 g. (Found: C, 64.3; H, 4.4; $C_{16}H_{10}O_5, H_2O$ requires C, 64.0; H, 4.0%).

SUMMARY

Using N-bromosuccinimide, a synthesis of 7:7'-dihydroxychromeno-(3:4':2:3) chromone has been effected. 7:2':4'-Triacetoxy-2-methyl isoflavone is brominated to give the 2-bromomethyl isoflavone which is cyclized, after hydrolysis, to the corresponding chromenochromone.

REFERENCES

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2. Mitter and Maitra .. *Jour. Ind. Chem., Soc.*, 1936, **13**, 236.
3. King and Neill .. *Jour. Chem. Soc.*, 1952, 4752.