NUCLEAR OXIDATION IN FLAVONES AND RELATED COMPOUNDS

Part XXX. A New Synthesis of Asarone

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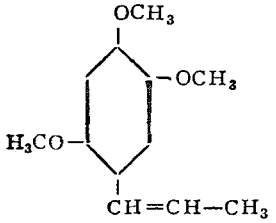
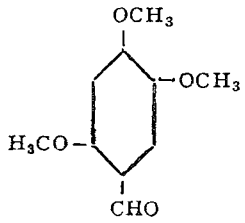
Received June 16, 1950

Asarone (I) is an important isomer of elemicin and occurs in the ethereal oils of *Asarum arifolium*, *Asarum europeum* and *Acorus calamus*. Its constitution was established and its first synthesis was effected by Gattermann and Eggers.[1] They heated for this purpose asarylic aldehyde (II) with propionic anhydride and sodium propionate in a sealed tube for 7 hours



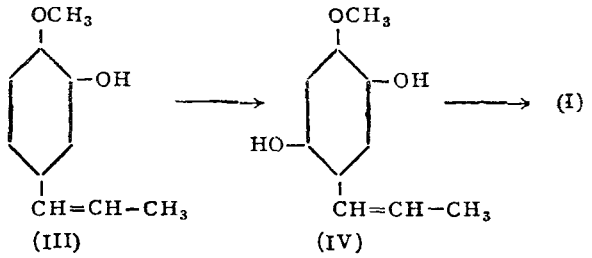
(I)



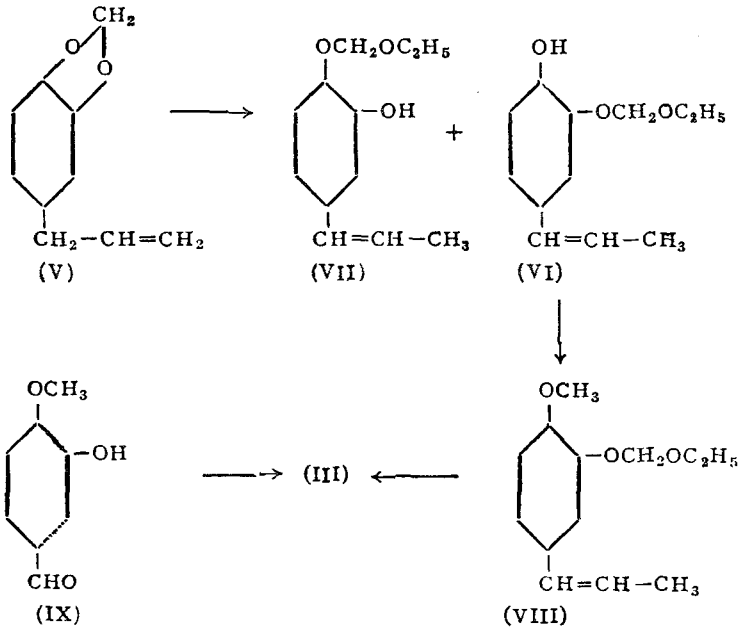
(II)

at 150°. More recently Bert[2] has effected the synthesis starting from the trimethyl ether of hydroxy-hydroquinone and 1 : 3-dichloro-propylene.

In Part XXIV[3] of this series the idea was discussed that among allyl and propenyl benzene compounds present in essential oils, the catechol derivatives represent more fundamental stages in biogenesis, and the synthesis of elemicin and myristicin (pyrogallol derivatives) was carried out conveniently starting from eugenol and using the two stage process of ortho oxidation. Asarone has a fully methylated hydroxy-quinol unit and has a propenyl side chain. For its preparation the appropriate catechol derivative would be isochavibetol (III). Though this particular compound does not occur in nature, its isomer chavibetol is found in betel leaves. The isomerisation to isocompounds is fairly facile in this series. It is therefore suggested that asarone (I) is evolved in plants from isochavibetol (III) by a process involving para nuclear oxidation (IV) and methylation. This transformation has now been effected in the laboratory and it represents a new synthesis of asarone. The synthetic compound agrees in its properties and in its derivatives with natural asarone. It may be mentioned here that the method of nuclear oxidation has been successfully applied in our laboratory for the preparation of asaronic acid, aldehyde and related compounds.[7]



Isochavibetol (III) was obtained first by the isomerisation of chavibetol with alcoholic potash.[4] It was also made by the transformation of safrole[5] (V). By the action of ethyl alcoholic potash on safrol (V) a mixture of two phenols, ethoxy isoeugenol (VI) and ethoxy isochavibetol (VII) was obtained. The mixture was separated through the benzoates. The former (VI) was subsequently methylated with dimethyl sulphate and alkali and the product (VIII) hydrolysed with alcoholic hydrochloric acid when isochavibetol (III) was produced. Later it was prepared (10% yield) by



the application of the Grignard reaction using isovanillin (IX) and excess of magnesium ethyl iodide.[6] For our present purpose we have adopted the convenient process in which isovanillin (IX) is condensed with sodium propionate and propionic anhydride. The product is isochavibetol propionate and on hydrolysis yields isochavibetol (III) agreeing in its properties and derivatives with the natural product.

Experimental

Isochavibetol (III):

Isovanillin (2 g.), propionic anhydride (8 c.c.) and freshly fused sodium propionate (2 g.) were heated together in an oil-bath at 140–50° for seven hours. The resulting liquid was then poured into ice water (150 c.c.) and left overnight. A semi-solid mass was thus obtained. It was dissolved in ether, the ether extract shaken well with excess of sodium carbonate solution, washed with water and then distilled to remove the ether. The residue was insoluble in aqueous alkali and should thus be the propionate of isochavibetol. It was refluxed with alcoholic potash for half an hour, the alcohol removed under reduced pressure and the residue treated with dilute hydrochloric acid. The dark reddish brown viscous liquid collecting at the bottom was dissolved in ether and the ether extract washed with water and dried over anhydrous sodium sulphate. On distilling off the ether an oily liquid was left behind which soon solidified to a pale brown solid mass (1 g.). It crystallised from ethyl acetate-benzene mixture to give colourless rectangular rods melting at 95–96°. It had a characteristic odour, gave a yellow solution with aqueous sodium hydroxide and a bluish green colour with alcoholic ferric chloride. (Found: C, 72·9; H, 7·1; $C_{10}H_{12}O_2$ requires C, 73·2; H, 7·3%.) The acetate crystallised from ethyl acetate-petroleum ether mixture as clusters of colourless needles melting at 99–100°.

3 : 6-*Dihydroxy*-4-*methoxy*-1-*propenyl benzene (IV)*:

To a stirred ice-cooled solution of isochavibetol (4 g.) in aqueous sodium hydroxide (3 g. in 60 c.c.) a solution of sodium persulphate (6 g.) in water (60 c.c.) was added drop by drop in the course of one and a half hours. After 24 hours the solution was acidified to congo red when a dark semi-solid containing unchanged isochavibetol separated. This was removed by shaking thrice with ether, 75 c.c. each time (ether solution A). Concentrated hydrochloric acid (25 c.c.) and sodium hydrogen sulphite (0·5 g.) were then added to the aqueous solution which was heated on a boiling water-bath for fifteen minutes and cooled when a dark brown precipitate was obtained. It was filtered, the filtrate saturated with sodium chloride and extracted with ether repeatedly. On evaporating the ether some more of the brown solid was obtained. The total yield was 0·2 g. About half of the isochavibetol could be recovered unchanged from ether solution A. The experiment was repeated a number of times to get material enough for characterisation and for the subsequent methylation experiment.

The dihydroxy compound was crystallised from ethyl acetate to give colourless rectangular prisms melting at 136°. It was soluble in alkali forming

a brownish yellow solution which slowly changed to darker brown. With alcoholic ferric chloride it gave a transient green colour with a tinge of blue changing to brown very quickly. An alcoholic solution of it turned brown in a few minutes on adding an alcoholic solution of *p*-benzoquinone. (Found: C, 66·6; H, 6·7; $C_{10}H_{12}O_3$ requires C, 66·6; H, 6·7%.)

Asarone (*I*):

The above dihydroxy compound (0·5 g.) was methylated by refluxing in anhydrous acetone solution (100 c.c.) with dimethyl sulphate (0·8 c.c.) and anhydrous potassium carbonate (3 g.) for six hours. The solution was filtered and the potassium salts washed with acetone. The solvent was distilled off from the combined filtrate and washings, when an oily liquid was left behind. It was dissolved in ether (50 c.c.) and the ether solution shaken twice with aqueous alkali (20 c.c.), washed with water and dried over anhydrous sodium sulphate. On distilling off the ether, a viscous brown liquid was left behind which soon solidified. It was dissolved in light petroleum and the solution allowed to evaporate gradually. Colourless needles were thus deposited on the sides of the test-tube when the solution was concentrated to half its original volume. The crystals of asarone thus obtained were filtered. The melting point was found to be 62–3°. (Found: C, 69·4; H, 7·8; $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%.) The dibromide was prepared by treating the asarone sample in chloroform solution in the cold with excess of bromine. The solvent was then distilled off and the residue crystallised from acetone when it was obtained as colourless plates melting at 86–7° with decomposition.

Summary

Based on considerations of biogenesis asarone is now synthesised from isochavibetol by para nuclear oxidation with alkaline persulphate and subsequent methylation. Isochavibetol needed for this purpose is conveniently prepared by the condensation isovanillin with propionic anhydride and sodium propionate.

References

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