CCXII.—*A Synthesis of Safrole and* o-*Safrole.*

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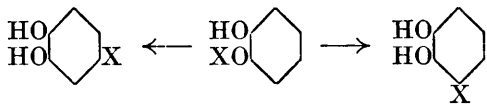
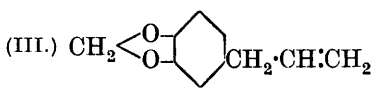
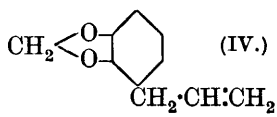
No direct synthesis of safrole has been recorded, the most recent attempt being that of Baker and Robinson (J., 1925, **127**, 1424), who distilled the product of the action of silver oxide and water upon γ-piperonylpropyltrimethylammonium iodide, but obtained *iso*safrole, the double bond moving into the position of greater stability. Kawai (*Sci. Papers Inst. Phys. Chem. Res.*, 1925, **3**, 263) has shown that the monoallyl ether of pyrocatechol undergoes the Claisen rearrangement to give an oil which he considered to be a mixture of 3- and 4-allyl-1 : 2-dihydroxybenzene, the change taking place in the following manner (X = CH_2·CH:CH_2) :

(II.)  (I.)

This matter has now been reinvestigated and, by repeated fractionation of the product of the rearrangement, both of the above isomerides have been isolated in a pure state as colourless, crystalline solids melting at 28° and 48° respectively. As further confirmation of the course of the Claisen migration, it has been found that the properties of the higher-melting isomeride (II) are in accord with those assigned to the " 4-allylbrenzcatechin " which Schimmel and Co. (*Centr.*, 1907, II, 1741) isolated in small quantity from betel-leaf oil from Java. The second isomeride, 1 : 2-*dihydroxy*-3-*allylbenzene* (I), has not previously been described.

In order to convert these substances into safrole (III) and *o*-safrole (IV), respectively, methylenation was carried out, with

(III.)   (IV.)

moderately good yields, by gently refluxing them with methylene iodide and anhydrous potassium carbonate in dry acetone solution. By employing such mild conditions, any change into the isomeric *iso*safroles during the course of the reaction was inhibited. The identity of the synthetic product with naturally occurring safrole has been established by preparing the pentabromo-derivative (m. p. 169°) and the acetamido-derivative (m. p. 162—163°) and comparing these with the same derivatives from natural safrole. The properties of the hitherto unknown isomeride *o-safrole* (IV)

(which resembles safrole in odour and in many other ways) have been recorded.

The process of methylenation described above takes place very smoothly without formation of tarry products and may prove to be valuable in other cases of this kind.

Experimental.

Mono- and Di-allyl Ethers of Pyrocatechol.—Pyrocatechol (132 g.) and pure allyl bromide (144 g.) were dissolved in pure dry acetone (220 c.c.), finely powdered, freshly heated potassium carbonate (170 g.) was added gradually with constant shaking, and the whole refluxed for 6—8 hours on the water-bath, the condenser being fitted with a calcium chloride tube (compare Kawai, *loc. cit.*). After removal of the acetone, addition of water and dilute sulphuric acid, and extraction with ether, the monoallyl ether and unchanged pyrocatechol were removed by washing the extract with dilute alkali solution, and the ethereal solution was then dried with anhydrous sodium sulphate and evaporated. The yield of pure diallyl ether was 43 g. (b. p. 124—125·5°/13 mm.). The alkali washings were immediately acidified and the oil was taken up in chloroform. After being repeatedly washed with water to remove pyrocatechol, the chloroform was evaporated and the oil distilled, yielding 90 g. of pure monoallyl ether, b. p. 107·5—109°/15 mm. The yields of both ethers were considerably higher than those recorded by Kawai under almost analogous conditions.

Molecular rearrangement. The monoallyl ether (92 g.) was heated in a flask, fitted with a ground-in condenser, in a paraffin bath at 170—180°; the inner temperature suddenly rose to 265° with momentary boiling, the colour of the liquid changing to red. After cooling, the product was fractionated under 15—16 mm. and fractions, b. p. 142—152° (66·2 g.) and 152—160° (17·2 g.), were collected, leaving a resinous, non-volatile residue (9 g.). The second fraction solidified on standing and consisted chiefly of 1 : 2-dihydroxy-4-allylbenzene, melting at 40—41° with previous softening. Kawai noticed the formation of some crystals in his higher fraction (b. p. 155—160°/16 mm.) and suggested that they were due to pyrocatechol which had been set free during the rearrangement (compare Claisen, *Annalen*, 1913, **401**, 21). In the present instance, however, no pyrocatechol was observed and it is probable that his crystals were those of 1 : 2-dihydroxy-4-allylbenzene.

After repeated systematic refractionation of the above two fractions, both isomerides were isolated in a pure condition, the proportion of 1 : 2-dihydroxy-3-allylbenzene to its isomeride in the rearranged product being approximately 5 to 4.

1 : 2-*Dihydroxy*-4-*allylbenzene* (II) is a colourless, waxy, crystalline solid soluble in water and most other solvents, but sparingly soluble in petroleum. It forms colourless needles, m. p. 48°, from benzene–light petroleum and boils at 147—149°/10 mm. and at 156—158°/16 mm. (Found: C, 72·1; H, 6·8. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). The dibenzoyl derivative (Schotten-Baumann) separates from light petroleum in colourless prisms, m. p. 71°. These properties clearly indicate that the substance is identical with the "allylbrenzcatechin" isolated from Java betel-leaf oil (*loc. cit.*).

1 : 2-*Dihydroxy*-3-*allylbenzene* (I) is best purified by distillation under reduced pressure and has b. p. 143·5—145°/15 mm. If allowed to crystallise slowly, it separates in large, colourless, flat prisms, m. p. 28°, but it has a tendency to remain liquid below this temperature. Owing to this property, it was not found possible to recrystallise it satisfactorily. It dissolves readily in most solvents except petroleum, whilst in water it is not as soluble as its isomeride (Found: C, 72·1; H, 6·5. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%).

It resembles its isomeride in having a phenolic odour and in aqueous solution it gives with ferric chloride an olive-green colour, changing to wine-red on addition of sodium carbonate.

The *dibenzoyl* derivative separates from light petroleum in colourless prisms, m. p. 60—61° (Found: C, 77·1; H, 5·2. $C_{23}H_{18}O_2$ requires C, 77·1; H, 5·0%).

Safrole (III).—1 : 2-Dihydroxy-4-allylbenzene (10 g.) and methylene iodide (18 g.) were dissolved in pure dry acetone (35 c.c.) and finely powdered, freshly ignited potassium carbonate (20 g.) was gradually added with shaking to prevent caking. After gently refluxing on the water-bath for 12 hours, the acetone was removed, the product was made acid with dilute sulphuric acid and extracted with ether, and the ethereal solution was repeatedly washed with dilute aqueous sodium hydroxide and finally with water, dried over sodium sulphate, and evaporated. On carefully distilling the residue under reduced pressure, methylene iodide first passed over; when this had been completely removed, a fraction, b. p. 100—101·5°/10—11 mm., consisting of 2·5 g. of a clear, colourless oil, was collected. This was identified as safrole by its characteristic odour and by preparing its *pentabromo*-derivative by gradually adding excess of bromine below 0° and allowing the mixture to stand for some hours; the solid substance which had separated, after recrystallising from ethyl alcohol, melted at 169°, and a mixed melting point with the derivative prepared from ordinary safrole showed no depression. The oil had $n_D^{20°}$ 1·5381 (Found: C, 74·2; H, 6·4. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%). As an additional

proof of identity, 1·35 g. of the synthetic substance were nitrated under the conditions laid down by Foulds and Robinson (J., 1914, **105**, 1963), the nitro-derivative was reduced with tin and hydrochloric acid, and the crude 6-aminosafrole acetylated; the acetyl derivative crystallised from methyl alcohol in colourless needles, m. p. 162—163° (Found: C, 65·5; H, 6·0. Calc. for $C_{12}H_{13}O_3N$: C, 65·7; H, 5·9%), and a mixed melting-point determination with the corresponding derivative from naturally occurring safrole showed no depression.

o-*Safrole* (IV).—1 : 2-Dihydroxy-3-allylbenzene (20 g.), methylene iodide (36 g.), potassium carbonate (40 g.), and acetone (70 c.c.) were gently refluxed for 14 hours, and the product was treated in a manner similar to that described above in the synthesis of safrole. Methylene iodide was removed under reduced pressure, and the remainder (boiling over 1·5°) collected separately. Yield, 7 g. It was redistilled and collected at 102·5—103°/13 mm. (Found: C, 74·3; H, 6·2. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%). It boils at 106—107°/16 mm. and at 226—227°/762 mm.

o-Safrole is a colourless, mobile oil which does not crystallise at −20° and has $n_D^{20°}$ 1·5359. It has an agreeable odour, similar to, but not so pronounced as, that of safrole (compare the respective odours of *o*-piperonal and piperonal; Perkin and Trikojus, J., 1926, 2927). On the addition of excess of bromine to *o*-safrole cooled below 0°, a vigorous reaction occurs; the product, which solidifies on standing over-night, is washed with ethyl alcohol and crystallised from the same solvent, in which it is only sparingly soluble. The resulting *pentabromo*-derivative separates in colourless prisms, m. p. 154°, and the yield is almost quantitative (Found: Br, 71·8. $C_{10}H_7O_2Br_5$ requires Br, 71·6%).

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