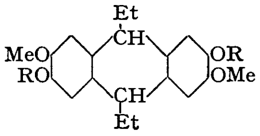
178. *The Constituents of Natural Phenolic Resins. Part XXI.* The Structure of Di*iso*eugenol.*

By Neville J. Cartwright and Robert D. Haworth.

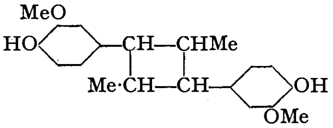
Structure (I; R = H) suggested for di*iso*eugenol in 1931 has been disproved by the synthesis of a tetramethoxyanthracene derivative of structure (I; R = Me) which, in its ready dehydrogenation, differs markedly from di*iso*eugenol dimethyl ether. Structure (III; R = H) is rejected because (*a*) such a lignan structure would be inconsistent with the difficulties experienced in the dehydrogenation of di*iso*eugenol derivatives, and (*b*) synthetic analogues of (III; R = Me) give colour reactions which differ from those shown by di*iso*eugenol dimethyl ether. Structure (IV; R = H) recently advanced by Müller *et al.* is regarded as the most likely structure for di*iso*eugenol for the following reasons. The ketone (VIII) has been synthesised and shown to be identical with the red oxidation product of di*iso*eugenol dimethyl ether which Haworth and Mavin (*J.*, 1931, 1363) had regarded as an anthrone derivative. The hydrindenes (IX) and (IV; R = Me) have been synthesised; both resist dehydrogenation and both give colour reactions resembling those exhibited by di*iso*eugenol dimethyl ether. The hydrindene (IV; R = Me) is, however, not identical with di*iso*eugenol dimethyl ether, but the difference may be stereochemical.

The constitution of di*iso*eugenol has recently been the subject of eight communications by Müller *et al.* [(i) *Ber.*, 1942, **75**, 692; (ii) *ibid.*, p. 891; (iii) *ibid.*, 1943, **76**, 855; (iv) *ibid.*, p. 1061; (v) *ibid.*, p. 1119; (vi) *ibid.*, 1944, **77**, 6; (vii) *ibid.*, p. 12; (viii) *ibid.*, p. 159] and as conclusions similar to our present views have been reached, it is desirable, in spite of the incomplete nature of our work, to place on record our contributions to this problem.

In 1931, Haworth and Mavin (*J.*, 1931, 1363) suggested that di*iso*eugenol had structure (I; R = H) instead of the *cyclo*butane structure (II) proposed by earlier workers. The introduction of this anthracene structure rested very largely on the isolation of 2 : 3 : 6 : 7-tetramethoxyanthraquinone from the products of the chromic acid oxidation of di*iso*eugenol dimethyl ether, but Szeki (*Annalen*, 1933, **507**, 197) and Szeki and Haraszti (*ibid.*, **508**, 294), disregarding this evidence, adhered to the *cyclo*butane structure (II). Müller *et al.* [(i) and (ii)] first proposed the lignan structure † (III; R = H) but in later communications they abandoned this in favour of the hydrindene structure (IV; R = H) which resembles the metanethole structure suggested by Baker and Enderby (*J.*, 1940, 1094).



(I.)



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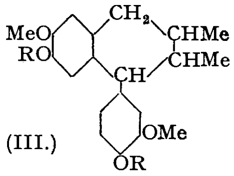

(III.)

Müller's conclusions depend to a great extent upon the oxidation to *o*-veratroylveratric acid and upon the interpretation of the properties of a hydroxy-ketone obtained as one of the products of oxidation of di*iso*eugenol dimethyl ether. This substance, formulated as (V) in his later papers, is readily converted into a red anhydro-derivative, which is now regarded as an indene derivative, but for which Haworth and Mavin (*loc. cit.*) had tentatively proposed an anthrone structure. In our opinion Müller's work is inconclusive; the following observations made over a period of years, although equally inconclusive, have led us quite independently to the view that di*iso*eugenol is best represented by the hydrindene structure (IV; R = H).

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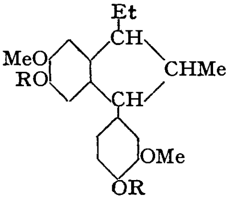
* The last communication (*J.*, 1944, 535) of this series was erroneously numbered as Part XIX instead of Part XX.

† Oliverio (*Gazzetta*, 1943, **73**, 270) reports that he suggested the lignan formula (III; R = H) for di*iso*eugenol in 1937.

In 1937, unpublished work with Miss W. Robson, B.Sc., showed that di*iso*eugenol dimethyl ether resembled 2 : 3 : 6 : 7-tetramethoxy-9 : 10-dihydroanthracene in absorption spectra, both



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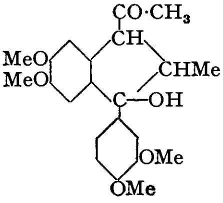

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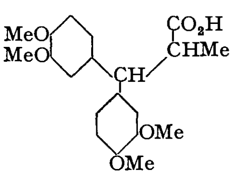
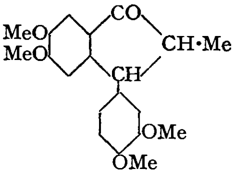


(VI.)

showing maximum absorption at a wave-length of 2850 A., but structural similarity cannot be inferred, as the veratrole nucleii present in both structures are responsible for the absorption. At this stage, unsuccessful attempts were made to dehydrogenate di*iso*eugenol dimethyl ether with lead tetra-acetate, palladium black, and selenium and aluminium chloride, and numerous later efforts have been equally unsuccessful. The dihydroanthracene structure (I) can now be discarded, because Müller's observation that an anthracene derivative, and not a dihydroanthracene, is obtained by the condensation of veratrole and propaldehyde, indicates that dihydroanthracenes are characterised by an instability which is not shown by di*iso*eugenol dimethyl ether. In addition, we have reduced the highly fluorescent 2 : 3 : 6 : 7-tetramethoxy-9 : 10-diethylanthracene by means of sodium and amyl alcohol to 2 : 3 : 6 : 7-*tetramethoxy*-9 : 10-*diethyl*-9 : 10-*dihydroanthracene* (I; R = Me), m. p. 148°. Unlike di*iso*eugenol dimethyl ether, this was readily dehydrogenated with lead tetra-acetate in glacial acetic acid solution to the corresponding anthracene derivative, and when a drop of concentrated nitric acid was added to its acetic acid solution a red coloration with a permanent blue reflex was obtained which differed from the cherry-red test given by di*iso*eugenol dimethyl ether.

Our failures, mentioned above, to dehydrogenate di*iso*eugenol dimethyl ether are equally inconsistent with the 1-phenyl-1 : 2 : 3 : 4-tetrahydronaphthalene structure (III); the expected product, dehydroguaiaretic acid dimethyl ether, is sparingly soluble in alcohol or acetic acid, and its isolation from complex selenium dehydrogenation mixtures has previously (*J.*, 1938, 1681) been accomplished without difficulty. Attempts to synthesise the structure (III; R = Me) by the action of methyl-alcoholic hydrogen chloride, glacial acetic, and hydrochloric acid mixtures, 100% formic acid, sulphuric acid of various strengths, acetic and sulphuric acid mixture, or phosphoric oxide in toluene on guaiaretic acid dimethyl ether, have yielded unchanged materials, frequently in high yield but sometimes contaminated with intractable oils. Other routes investigated included : (*a*) the conversion of *iso*lariciresinol dimethyl ether (*J.*, 1937, 386) into the corresponding 2 : 3-bischloromethyl derivative for subsequent reduction; (*b*) dehydration and reduction of 4-hydroxy-6 : 7-dimethoxy-1-veratryl-2 : 3-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (*J.*, 1938, 1681); (*c*) reduction of 6 : 7-dimethoxy-1-veratryl-3-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylic acid (*J.*, 1938, 811) and the isomeric 2-methyl-1 : 2 : 3 : 4-tetrahydronaphthalene-3-carboxylic acid (*loc. cit.*). These experiments gave either unchanged material or unrecognisable oils, and although these oils may contain diastereoisomeric forms of the structure (III; R = Me), it is unlikely that they contain the highly crystalline di*iso*eugenol dimethyl ether. In addition, 6 : 7-*dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*, synthesised from veratrole and ethyl β-hydroxymethylene-propionate, gave colour reactions differing markedly from those of di*iso*eugenol dimethyl ether, and it was smoothly dehydrogenated by lead tetra-acetate to 6 : 7-dimethoxy-1-veratryl-naphthalene, m. p. 160° (*J.*, 1935, 636).

These experiments led us to reject the dihydroanthracene and tetrahydronaphthalene structures (I) and (III), respectively, in favour of the hydrindene structure (IV), and synthetical confirmation of the latter has been sought. Condensation of veratrole and ethyl α-hydroxymethylenepropionate yielded ββ-*diveratryl-α-methylpropionic acid* (VI), m. p. 175°, and the corresponding acid chloride was converted into 5 : 6-*dimethoxy*-3-*veratryl*-2-*methylhydrindone* (VII), m. p. 116°. This cyclic ketone was dehydrogenated by heating with palladium at 250° to 5 : 6-*dimethoxy*-3-*veratryl*-2-*methyl*-1-*indone* (VIII), m. p. 194—195°, identical with the orange-red ketone which Haworth and Mavin (*loc. cit.*) previously regarded as 2 : 3 : 6 : 7-tetramethoxy-9-ethylanthrone. The ketone (VII) was readily reduced by Clemmensen's method to give 5 : 6-*dimethoxy*-3-*veratryl*-2-*methylhydrindene* (IX), m. p. 117°. The ketone (VII) also reacted smoothly with ethylmagnesium iodide to yield the oily *indene* derivative (X), which combined with excess Grignard reagent with the formation of a precipitate and the evolution of ethane. This reaction supports the indene structure (X) and excludes an alternative 1 : 3-dimethyldihydronaphthalene formula arising from pinacolic change from the intermediate carbinol. The indene derivative (X) was reduced in acetic acid with a very active platinic oxide catalyst to give 5 : 6-*dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylhydrindene* (IV; R = Me), m. p. 105°, depressed to 95—98° by admixture with a specimen of di*iso*eugenol dimethyl ether, m. p. 105°. The hydrindene (IV; R = Me), like (IX) and di*iso*eugenol dimethyl ether, resisted dehydrogenation and gave a permanent cherry-red colour with a transient purple reflex when a drop of concentrated nitric acid was added to its solution in glacial acetic acid.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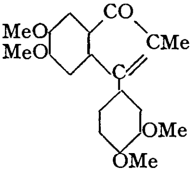
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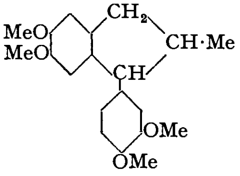
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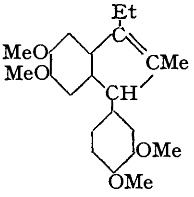
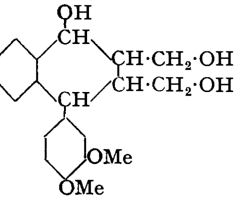

(X.)

Structure (IV) permits of four racemic modifications. Ciamician and Silber (*Atti R. Accad. Lincei*, 1909, **18**, 1216) converted the readily accessible form of di*iso*eugenol dimethyl ether, m. p. 105°, into an isomer, m. p. 96°, by the action of iodine, and Müller *et al.* (*loc. cit.*) have obtained a third isomer, m. p. 100°, by more indirect methods. These isomeric forms were not available for comparison purposes but the synthetic hydrindene derivative (IV; R = Me), m. p. 105°, is possibly an isomeric modification of di*iso*eugenol dimethyl ether, although efforts to convert it into a diastereoisomeric form by the action of methyl-alcoholic hydrogen chloride have failed.

The oxidation of di*iso*eugenol dimethyl ether to 2 : 3 : 6 : 7-tetramethoxyanthraquinone is in no way inconsistent with the hydrindene structure (IV; R = Me). Dreyfuss (*Gazzetta*, 1936, **66**, 96) has shown that this anthraquinone, together with *o*-veratroylveratric acid and the lactone of 3 : 3′ : 4 : 4′-tetramethoxybenzhydrol-6-carboxylic acid, is obtained by the oxidation of *iso*olivil dimethyl ether (XI). Structure (XII) is postulated as a possible intermediate stage in the conversion into the anthraquinone, and a similar mechanism could obviously be formulated for the oxidation of the hydrindene (IV; R = Me).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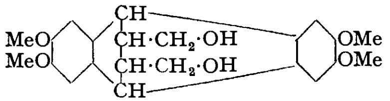
(XII.)

EXPERIMENTAL.

2 : 3 : 6 : 7-*Tetramethoxy*-9 : 10-*diethyl*-9 : 10-*dihydroanthracene* (I; R = Me).—2 : 3 : 6 : 7-Tetramethoxy-9 : 10-diethylanthracene (0·3 g.) (Müller, *loc. cit.*, ii) in boiling amyl alcohol (25 c.c.) was treated with sodium (2 g.). After ½ hour's refluxing, water was added, the amyl alcohol was separated and dried, and the solvent removed under reduced pressure. Ethyl alcohol was added to the residue, and the unreduced anthracene derivative (0·15 g.) was collected and the filtrate concentrated; the 9 : 10-dihydroanthracene (I; R = Me) crystallised from methyl alcohol in colourless, dense prisms (0·06 g.), m. p. 147—148° (Found: C, 73·7; H, 7·9; OMe, 34·5. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·7; OMe, 34·8%), which gave the colour reaction described on p. 949.

Diacetyl Derivatives of Guaiaretic and Dihydroguaiaretic Acids.—Crude extract (5 g.) of guaiacum resin, fused sodium acetate (5 g.), and acetic anhydride (15 c.c.) were heated on the water-bath for 2 hours. Water was added, and the product was collected and fractionally crystallised from ethyl alcohol. *Diacetyl dihydroguaiaretic acid* separated from alcohol in stout irregular prisms, m. p. 112° (Found: C, 69·5; H, 7·1. $C_{24}H_{30}O_6$ requires C, 69·6; H, 7·3%), which gave no colouration with concentrated sulphuric acid. *Diacetyl guaiaretic acid* separated from a small bulk of alcohol in slender hexagonal prisms, m. p. 86—87° (Found: C, 69·2; H, 6·8. $C_{24}H_{28}O_6$ requires C, 69·8; H, 6·8%), which gave a deep red colour with concentrated sulphuric acid and absorbed the theoretical amount of hydrogen.

6 : 7-*Dimethoxy*-1-*veratryl*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-3-*carboxylic Acid.*—The conversion of the lactone of β-veratroyl-α-veratrylidene-*n*-butyric acid into methyl 6 : 7-dimethoxy-1-veratryl-2-methylnaphthalene-3-carboxylate (*J.*, 1938, 811) was best effected with methyl-alcoholic hydrogen chloride, saturated at 0°, and the methyl ester has m. p. 198° and not 178° as previously reported. The corresponding acid was reduced in faintly alkaline solution by boiling for 4 hours with 4% sodium amalgam (150 parts), during which time a stream of carbon dioxide was passed through the solution.

Acidification gave 6 : 7-*dimethoxy*-1-*veratryl*-2-*methyl*-1 : 2-*dihydronaphthalene*-3-*carboxylic acid,* which crystallised from methyl alcohol in clusters of fine needles, m. p. 178—179° (Found : C, 68·4; H, 6·4. $C_{22}H_{24}O_6$ requires C, 68·8; H, 6·3%), rapidly decolorising permanganate in cold alkaline solution. Reduction of this dihydro-acid was effected in acetic acid solution by hydrogen in presence of palladised charcoal; the corresponding *tetrahydronaphthalene*-3-*carboxylic acid* separated from methyl alcohol in silky needles, m. p. 162° (Found : C, 68·1; H, 6·9. $C_{22}H_{26}O_6$ requires C, 68·4; H, 6·8%), which were unaffected by cold permanganate. The corresponding acid chloride was not obtained pure, and Rosenmund reduction to the aldehyde was not realised.

4-*Keto*-6 : 7-*dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—A mixture of concentrated sulphuric acid (11 c.c.) and glacial acetic acid (11 c.c.) was gradually added, with ice cooling, to a mixture of ethyl β-hydroxymethylenepropionate (4 g.), veratrole (10 g.), and glacial acetic acid. After 18 hours, water was added and the product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (35 c.c.). Removal of the solvent and acidification gave the crude acid (9 g.) which was refluxed with excess of thionyl chloride in chloroform. The solvent was evaporated, the residue dissolved in nitrobenzene (50 c.c.), and aluminium chloride (8 g.) added. After 12 hours, dilute sulphuric acid was added, and the nitrobenzene removed in steam. The *ketone*, isolated with chloroform and washed with dilute sodium hydroxide, was distilled at 0·1 mm. (bath temp. 270°); the distillate (6 g.) crystallised from methyl alcohol in prisms, m. p. 137—138° (Found : C, 69·9; H, 6·5. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%), which gave a 2 : 4-dinitrophenylhydrazone, m. p. 270° (decomp.).

6 : 7-*Dimethoxy*-1-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The above ketone (1 g.) was reduced by Clemmensen's method, and the product was distilled at 0·01 mm. and crystallised first from aqueous acetone and then from ligroin; clumps of fine needles, m. p. 76° (Found : C, 73·2; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·2; H, 7·3%), were obtained, which dissolved in concentrated sulphuric acid to give a bright red solution. When nitric acid was added to an acetic acid solution of the tetrahydronaphthalene, a reddish purple colour was obtained which gradually changed through blue and green to orange. Dehydrogenation with lead tetra-acetate in acetic acid solution gave 6 : 7-dimethoxy-1-veratrylnaphthalene, m. p. 160°.

ββ-*Diveratryl*-α-*methylpropionic Acid* (VI).—A mixture of concentrated sulphuric acid (32·5 c.c.) and glacial acetic acid (32·5 c.c.) was added to a cooled solution of ethyl α-hydroxymethylenepropionate (13 g.) and veratrole (30 g.) in acetic acid (25 c.c.). After 12 hours the oily product, isolated with chloroform, was hydrolysed by refluxing for 2 hours with 10% methyl-alcoholic potassium hydroxide (100 c.c.). The *acid* (VI) crystallised from ethyl acetate in nodules of needles, m. p. 175° (Found : C, 66·7; H, 6·7; equiv., 362. $C_{20}H_{24}O_6$ requires C, 66·7; H, 6·7%; equiv., 360).

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methylhydrindone* (VII).—The above acid (VI) (5·5 g.), in chloroform (50 c.c.), and thionyl chloride (3·5 g.) were refluxed for 1 hour, and the solvent removed in a vacuum. Aluminium chloride (5·5 g.) was gradually added with cooling to a solution of the residue in nitrobenzene (50 c.c.) and, after 12 hours, the mixture was decomposed and the nitrobenzene removed in steam. The product, isolated with ether and washed with sodium hydroxide solution, crystallised from methyl alcohol in large prisms (5 g.), m. p. 116° (Found : C, 69·9; H, 6·4. $C_{20}H_{22}O_5$ requires C, 70·1; H, 6·4%), yielding an *oxime*, which separated from methyl alcohol in long glistening needles, m. p. 149—150° (Found : C, 67·3; H, 6·4. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%).

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*indone* (VIII).—The hydrindone (VII) (0·5 g.) and palladium black (0·1 g.) were heated for 1 hour at 250°, and the product was extracted with hot alcohol. Concentration of the extract gave orange-red prisms (0·05 g.), m. p. 189—192°, raised by recrystallisation from alcohol to 194—195°, undepressed by admixture with a specimen of the red compound, m. p. 193°, obtained by Haworth and Mavin (*loc. cit.*). The synthetic indone (VIII), and the product obtained by oxidation of di*iso*eugenol dimethyl ether, both dissolved in concentrated sulphuric acid to deep purple solutions.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methylhydrindene* (IX).—The hydrindone (VII) (4 g.) was reduced by Clemmensen's method; the product (3 g.) crystallised from methyl alcohol in long colourless needles, m. p. 117° (Found : C, 73·3; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·3%) depressed to 102° when mixed with a specimen of the ketone (VII). The *hydrindene* (IX) lacked ketonic properties, dissolved in concentrated sulphuric acid to a yellow solution, and gave the colour reaction described on p. **950**. Dehydrogenation with selenium or lead tetra-acetate did not yield recognisable products.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylindene* (X).—The hydrindone (VII) (5 g.) in benzene (50 c.c.) was gradually added to a solution of ethylmagnesium iodide, prepared from magnesium (1·0 g.) and ethyl iodide (7·5 c.c.) in ether (50 c.c.). After decomposition with ice and ammonium chloride, the product was heated at 180° for ½ hour with an equal weight of potassium hydrogen sulphate. The *indene* derivative (X), isolated with ether and washed with sodium bicarbonate solution, was obtained as a pale yellow resin, b. p. 195°/0·005 mm. (Found : C, 75·3; H, 7·7. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·4%), which reacted with ethylmagnesium iodide with formation of a precipitate and the evolution of ethane.

5 : 6-*Dimethoxy*-3-*veratryl*-2-*methyl*-1-*ethylhydrindene* (IV; R = H).—The indene derivative (X) (0·5 g.) in glacial acetic acid (10 c.c.) was shaken with hydrogen in the presence of freshly prepared Adams's platinic oxide catalyst (0·05 g.). The theoretical volume of hydrogen was absorbed in ½ hour. After filtration from the catalyst, water was added and the product was isolated with ether, and washed with sodium bicarbonate solution. Removal of the ether left an oil which rapidly solidified and then crystallised from methyl alcohol in elongated prisms, m. p. 105° (Found : C, 74·0; H, 8·1. $C_{22}H_{28}O_4$ requires C, 74·2; H, 7·9%) depressed to 95—98° when mixed with di*iso*eugenol dimethyl ether.* The

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* *Note, added* 12*th October,* 1946.—*Chemical Abstracts*, 1946, **40**, pp. 5041—5043, which has just been received, contains summaries of two additional papers by Müller and his co-workers, but the original papers (*Ber.*, 1944, **77**, 325, 343) are not available. In the second of these papers Müller describes the synthesis, by methods similar to ours, of the hydrindene (IV; R = Me), m. p. 105—106°. No mention of a direct comparison between the synthetic product and di*iso*eugenol dimethyl ether is included in the abstract, but, contrary to our observations, the title of the paper implies that identity is claimed.—R. D. H.

product, which did not decolorise permanganate in hot or cold acetone solution, was recovered after refluxing with methyl-alcoholic hydrogen chloride for 1¼ hours. It dissolved in concentrated sulphuric acid to an orange solution with a green fluorescence, and when a drop of concentrated nitric acid was added to its solution in glacial acetic acid, a red colouration with a purple reflex was obtained, which gradually changed to a pure cherry-red colour. Dehydrogenation with lead tetra-acetate in acetic acid or selenium at 280° yielded either unchanged material or unrecognisable tars.

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THE UNIVERSITY, SHEFFIELD, 10.

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