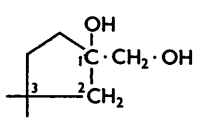
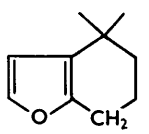
286. *Cafestol. Part II.* †*

By R. D. Haworth and R. A. W. Johnstone.

The conversion of cafestol into the tetrabasic acid (XII; R = R′ = H) has been effected by two alternative three-stage oxidation processes. Selenium dehydrogenation of this acid yielded, with other unidentified products, 4 : 5-benzindan-1-one (XV) and 1-ethyl-2-methylnaphthalene. Unless migration of alkyl groups is assumed the formation of the last compound cannot be explained on the basis of structure (V), recently suggested by Djerassi and his colleagues,[1] but the dehydrogenation may be readily interpreted on the basis of structure (IX) which is now advanced.

As a result of earlier work * it was concluded that cafestol had the molecular formula $C_{20}H_{28}O_3$ and probably contained the partial structures (I) and (II), although it was realised that quaternary carbon atoms postulated in each fragment depended on inconclusive evidence arising from the oxidative fission of the rings to acids containing hindered, and probably tertiary, carboxyl groups. Dehydrogenations of cafestol or of an anhydro-lactone derivative failed to throw light on the main skeleton although a diterpenoid structure was suspected. Djerassi and his co-workers [1] have recently subjected to selenium dehydrogenation a derivative of cafestol prepared by oxidising the partial structure (I) to the dibasic acid of partial structure (III). The isolation of 2-hydroxyphenanthrene and 1-ethyl-2-hydroxyphenanthrene from the dehydrogenation

(I) 



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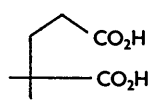


(III)

established both the pentacyclic nature of cafestol and the position of the furan ring, and led to the partial structure (IV). The five-membered ring glycol was considered to be attached to a bridgehead position as in structure (V) in order to account for several observations including (*a*) the infrared spectroscopic determination of one *C*-methyl group in epoxynorcafestadiene (VI) and (*b*) the formation of a tribromo-substitution product from epoxynorcafestanone (VII). The position of the angular methyl group was selected on the basis of an assumed biogenetic analogy with the phyllocladene system (VIII), but the location of the angular methyl group in phyllocladene has not been established.

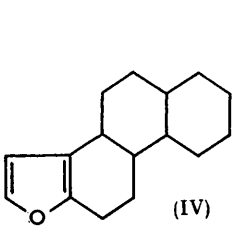
* Part I, *J.*, 1955, 1983.

† A preliminary account was published in *Chem. and Ind.*, 1956, 168.

[1] Djerassi, Bendis, and Sengupta, *J. Org. Chem.*, 1955, **20**, 1046; Bendis and Djerassi, *Chem. and Ind.*, 1955, 1483.

These investigations partly forestalled and overlapped our work which has confirmed the conclusions of Djerassi and his co-workers as far as the attachment of the furan ring and the five-membered ring glycol are concerned. But structure (V) does not contain the fragment (II) the presence of which was rendered probable by our earlier experiments, and for some time we had favoured the modified phyllocladene structure (IX) which is strongly supported by recent dehydrogenation experiments.

Epxoynorcafestadienone (X), prepared by the action of lead tetra-acetate on cafestol,[2] was converted by ozone into the dicarboxylic acid (XI), which was oxidised by potassium hypoiodite to the tetrabasic acid (XII; R = R′ = H). This acid (XII; R = R′ = H) was amorphous and probably composed of a mixture of epimeric forms. On methylation with diazomethane it gave a tetramethyl ester (XII; R = R′ = Me), which was hydrolysed by sodium hydroxide to the amorphous dimethyl ester (XII; R = Me, R′ = H), two ester groups resisting hydrolysis in accordance with the proposed structures. Similar products were obtained by an alternative route involving hypoiodite oxidation of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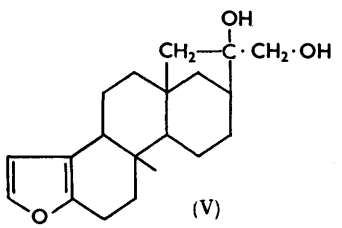
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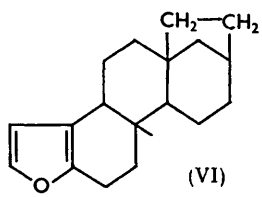
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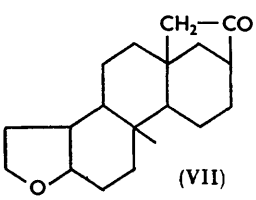
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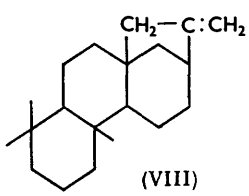
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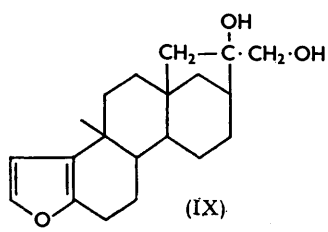
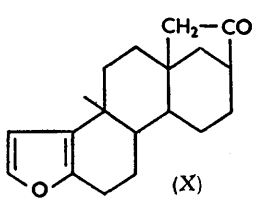
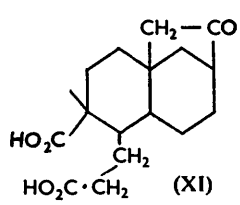

(IX)

epoxynorcafestadienone (X) to the dicarboxylic acid (XIII),[1] the dimethyl ester [1] of which was ozonised to the dibasic acid (XIV) yielding the tetramethyl ester (XII; R = R′ = Me) and dimethyl ester (XII; R = Me, R′ = H) on methylation and subsequent hydrolysis, respectively.


(X)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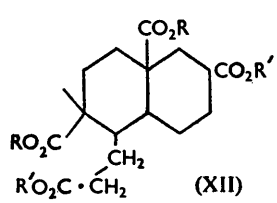
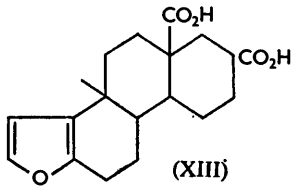

(XII)

The tetrabasic acid (XII; R = R′ = H) was dehydrogenated with selenium and the products separated by the combined use of the Girard-T reagent, vacuum distillation, chromatographic adsorption on alumina, and vapour-phase chromatography (cf. Experimental section).

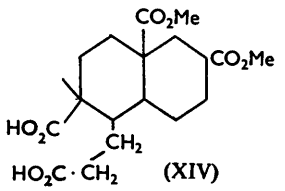
The ketonic fraction yielded 4 : 5-benzindan-1-one (XV) identified by comparison of the ketone and its 2 : 4-dinitrophenylhydrazone with synthetic specimens.[4] A small quantity of an unidentified six-membered ring ketone, $C_{15}H_{22}O_2$, was also isolated from the ketonic fraction. The benzindanone (XV) is obviously derived from the tetrabasic

[2] Wettstein, Fritzsche, Hunzicker, and Miescher, *Helv. Chim. Acta*, 1941, **24**, 332F.

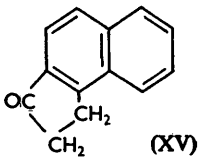
acid (XII; R = R′ = H) by cyclisation to the five-membered ring ketone, decarboxylation, and dehydrogenation, and its formation is not only consistent with structure (IX) and (XII; R = R′ = H) for cafestol and the tetrabasic acid, respectively, but proves



(XIII)



(XIV)



(XV)

that the methyl group in cafestol must be attached to an angular position from which it is eliminated during the dehydrogenation.

The main dehydrogenation product, however, was a hydrocarbon which showed three main regions of ultraviolet absorption at 220, 280, and 320 mμ characteristic of naphthalenes, and the ε value (794) of the 320 mμ band suggested a di- or tri-alkylated structure.[5] The hydrocarbon was identified as 1-ethyl-2-methylnaphthalene by comparison of the picrate and trinitrobenzene adduct with synthetic specimens. A viscous oil giving a crystalline but unidentified trinitrobenzene complex was also isolated, and small amounts of either 1- or 2-methylnaphthalene, and traces of two other non-identified products were detected by vapour-phase chromatography in the hydrocarbon fractions. The production of 1-ethyl-2-methylnaphthalene can be readily understood on the basis of formula (XII; R = R′ = H) for the tetrabasic acid, and, in the absence of migration phenomena, it establishes the position of the angular methyl group in cafestol (IX). In order to derive the hydrocarbon from other cafestol structures such as (V) it would be necessary to assume that the 2-methyl group was produced by reduction of a carboxyl group as has occasionally been observed [6] during selenium dehydrogenation experiments. This alternative explanation is, however, disposed of by the absence of polymethylnaphthalenes from the dehydrogenation products.

This structure (IX), like that suggested for methyl vinhaticoate, is not divisible into *iso*prene units. It is possible that these structures are derived from diterpenoid frameworks by migration of groups during the formation of the aromatic furan ring. Alternatively the structures may be derived by the combination of a pentose fragment with three *iso*pentane units.

Experimental

Cafestol, prepared from Green Santos Bourbon coffee beans as described in Part I, was oxidised by lead tetra-acetate to epoxynorcafestadienone,[2] which was ozonised and converted into the dibasic acid (XI).[3]

Oxidation of the Dibasic Acid (XI).—The dibasic acid (XI) (1·7 g.) in methanol (50 ml.) was treated simultaneously with a solution of iodine (5·5 g.) in methanol (50 ml.) and one of potassium hydroxide (4·5 g.) in methanol (50 ml.) containing water (3 ml.), both added dropwise and at room temperature during 1½ hr. with continuous stirring which was continued for 1½ hr. after completion of the addition. The mixture was poured into water (1 l.) containing a slight excess of sulphuric acid, the solution extracted several times with chloroform, and the combined extracts washed with successive small quantities of sodium thiosulphate solution and water. The chloroform solution was then extracted with dilute sodium hydroxide, from which the tetrabasic acid (XII; R = R′ = H) was recovered by acidification and isolated with chloroform. The colourless or light tan-coloured amorphous acid (1 g.) when methylated with

[3] Wettstein, Hunzicker, and Miescher, *Helv. Chem. Actr.*, 1943, **26**, 1197.
[4] Cook and Hewitt, *J.*, 1934, 365; Freser and Gates, *J. Amer. Chem. Soc.*, 1940, **62**, 2335.
[5] Morton and de Gouveia, *J.*, 1934, **916**; see also Friedel and Orchin, " Ultra-violet Spectra of Aromatic Compounds," John Wiley & Sons, New York.
[6] Windaus and Thiele, *Annalen*, 1936, **521**, 160; Wiesner, Armstrong, Bartlett, and Edwards, *J. Amer. Chem. Soc.*, 1954, **76**, 6068.

diazomethane in ether gave the *tetramethyl ester* (XII; R = R′ = Me) as a viscous liquid, b. p. 165° (bath temp.)/5×10^{-5} mm. (Found: C, 61·1; H, 7·8; MeO, 28·1. $C_{21}H_{32}O_8$ requires C, 61·1; H, 7·8; 4MeO, 30·0%).

Hydrolysis of the Tetramethyl Ester (XII; R = R′ = Me).—The tetramethyl ester (140 mg.) in methanol (6 ml.) was refluxed with N-sodium hydroxide (3 ml.) for 3 hr., and, after dilution with water (150 ml.), neutral material was removed in ether. The aqueous solution was acidified and extracted with ether–chloroform (1 : 2 v/v), and the extract dried (Na_2SO_4). Removal of the solvent and crystallisation from light petroleum (b. p. 40—60°) gave the dibasic *acid* (XII; R = Me, R′ = H) as micro-crystals, m. p. 58—63° (Found: equiv., 198. $C_{19}H_{28}O_8$ requires equiv., 192).

Oxidation of the Dimethyl Ester of Acid (XIII).—The dimethyl ester [1] (340 mg.) in ethyl acetate (50 ml.) was treated with sufficient ozone for the saturation of three double bonds at the temperature of acetone–solid carbon dioxide. The solvent was removed under reduced pressure at room temperature, and the ozonide heated on a steam-bath for 1 hr. with water (10 ml.) containing hydrogen peroxide (0·5 ml. of 100 vol.). The cooled solution was extracted with chloroform, the extract was washed with N-sodium hydroxide, and the washings acidified with dilute hydrochloric acid. The solution was extracted with chloroform, the extract dried (Na_2SO_4), and the solvent removed, leaving the dimethyl ester (XIV) as a colourless amorphous residue (290 mg.). This ester when esterified with ethereal diazomethane gave the tetramethyl ester (XII; R = R′ = Me), b. p. 160—170° (bath temp.)/5×10^{-5} mm., which was hydrolysed to the dibasic acid (XII; R = Me, R′ = H), m. p. 58—66° (Found: equiv., 194).

Reduction of the Dimethyl Ester of Acid (XIII).—The dimethyl ester (600 mg.) in methanol (10 ml.) and ethyl acetate (10 ml.) was hydrogenated at room temperature and pressure in the presence of 10% palladium–charcoal catalyst (700 mg.); the *tetrahydro-derivative* obtained by reduction of the furan ring was a viscous liquid, b. p. 180° (bath temp.)/0·7 mm. (Found: C, 69·0; H, 8·9. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·9%).

Action of Selenium on the Tetrabasic Acid (XII; R = R′ = H).—A typical experiment only is described. The tetrabasic acid (XII; R = R′ = H) (5·5 g.) was heated with selenium (9 g.) for 24 hr. at 330—340°. The mixture was extracted with ether, and the extract was washed successively with dilute sodium hydroxide solution and water and dried (Na_2SO_4). The ether was removed, the oily residue taken up in light petroleum (b. p. 40—60°), and the solution shaken with mercury (5 ml.) for 20 hr. to remove hydrogen selenide. The solvent was removed and the residue separated into ketonic and hydrocarbon fractions by treatment with Girard-T reagent.

The Girard-T extract was decomposed by contact with 0·5N-hydrochloric acid for 1 hr., and the ketonic products isolated with ether, dried, and sublimed at 160° (bath temp.)/10 mm. The sublimate yielded, after further sublimation and crystallisation from methanol, 4 : 5-benzindan-1-one as needles (15 mg.), m. p. 119—120°, alone or admixed with an authentic specimen,[4] and the ultraviolet spectrum showed maxima at 228 mμ (ε 28,180), 248 mμ (ε 30,900), and 280 mμ (ε 10,000). The 2 : 4-*dinitrophenylhydrazone* separated from benzene–ethanol in red needles, m. p. and mixed m. p. 300° (Found: N, 15·5. $C_{19}H_{14}O_4N_4$ requires N, 15·5%). The residue from the sublimation was recrystallised several times from ether and gave a small quantity of colourless needles, m. p. 196—197° (Found: C, 77·0; H, 9·6. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%), which showed in the infrared spectrum a single band at 1720 cm.$^{-1}$ indicative of six-membered ring carbonyl absorption. This *ketone*, m. p. 196—197°, which gave a yellow 2 : 4-dinitrophenylhydrazone, was not identical with that, m. p. 196—198°, prepared as described by Djerassi, Wilfred, Visco, and Lemin.[7]

The hydrocarbon fraction was an oil, which was taken up in light petroleum (b. p. 40—60°), adsorbed on a small column of alumina and separated by elution with ether into two fractions: (a) a colourless liquid with a faint blue fluorescence and a naphthalene odour and (b) a viscous yellow fluorescent liquid with an odour reminiscent of pinacol.

Fraction (a) was distilled at 85—100°/0·05 mm., and the small residue (X) added to fraction (b); the colourless distillate (250 mg.) was converted into the trinitrobenzene adduct which separated from methanol in yellow needles, m. p. 117° undepressed by admixture with the trinitrobenzene complex prepared from synthetic 1-ethyl-2-methylnaphthalene.[8] The

[7] Djerassi, Wilfred, Visco, and Lemin, *J. Org. Chem.*, 1953, **18**, 1449.

[8] Brunner and Grof, *Monatsh.*, 1934, **64**, 76; Kloetzel, *J. Amer. Chem. Soc.*, 1940, **62**, 1711; Adkins and Davies, *ibid.*, 1949, **71**, 2955.

adduct, which in the ultraviolet region showed bands at 228 mμ (ε 100,000), 280 mμ (ε 10,720), and 321 mμ (ε 6761), was decomposed by passing an ethereal solution through alumina, and gave 1-ethyl-2-methylnaphthalene as an oil showing peaks in the ultraviolet spectrum at 226 mμ (ε 70,790), 280 mμ (ε 6310), 319 mμ (ε 794), and which gave a picrate, m. p. and mixed m. p. 111°. The remainder of fraction (a) was investigated by vapour-phase chromatography.

Fraction (b) [and the small residue (X) from fraction (a)] was separated by fractional distillation into fraction (b i) (20 mg.), b. p. 100—120° (bath temp.)/0·05 mm., giving a very small amount of a trinitrobenzene adduct, m. p. 123°, and investigated further by vapour-phase chromatography, and fraction (b ii), a green-yellow fluorescent viscous oil (50 mg.), b. p. 160—180° (bath temp.)/0·05 mm., which gave a trinitrobenzene adduct, separating from methanol in orange needles, m. p. 130° (Found, on a small quantity: C, 56·9; H, 4·8%), which showed strong maxima in the ultraviolet region at 233, 255, 272, 285, 300, 319, 326, 329, and 335 mμ.

Vapour-phase Chromatography.—The column (100 cm. × 0·7 cm.) was packed with silicone high-vacuum grease on Celite 535 (0·4 : 1 w/w), and after model experiments with carefully purified synthetic naphthalenes the following conditions were adopted. The samples (less than 0·05 ml.) were introduced by means of a hypodermic needle, the column temperature was 212°, a carrier gas (nitrogen) flow rate of approx. 25 ml./min. and a pressure drop in the column of 170 mm. were used; the retention times (min.) were: mesitylene 7, 1-methyl- 21·5, 2-methyl- 22, 1-ethyl- 38, and 1-ethyl-2-methyl-naphthalene 41.

Fraction (a), mixed with a little mesitylene, gave the following peaks with a flow rate of 25 ml./min.

TABLE 1.

Peak	Retention time (min.)	Assignment	Quantity
1	7	Mesitylene	Standard
2	21·5	1- or 2-Methylnaphthalene	Small quantity
3	30	?	Trace
4	41	1-Ethyl-2-methylnaphthalene	Major product
5	50·5	?	Trace

Peaks 3 and 5 were present in extremely small quantities and were not identified; peak 3, however, is not 1- or 2-ethylnaphthalene.

Fraction (b i), mixed with a little mesitylene, gave the following peaks with a flow rate of 22 ml./min.

TABLE 2.

Peak	Retention time (min.)	Assignment	Quantity
1	7·5	Mesitylene	Standard
2	42·5	1-Ethyl-2-Methylnaphthalene identical with fraction 5 of Table 1	Trace
3	56·5		Small quantity but more than in Table 1

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