*Cafestol. Part I.**

By R. D. Haworth, A. H. Jubb, and J. McKenna.

[Reprint Order No. 6138.]

The molecular composition of cafestol, $C_{20}H_{28}O_3$, has been confirmed by the *X*-ray method, and the compound is shown to be pentacyclic. Suggestions by previous workers of presence of the $>C(OH)\cdot CH_2\cdot OH$ group in a five-membered carbocyclic ring, and of a 2 : 3-disubstituted furan nucleus attached to a six-membered carbocyclic ring have also been confirmed. A new series of degradation products is described and some partial structures are considered, but the complete structure of the framework is not yet known.

Cafestol, $C_{20}H_{28}O_3$, is the main constituent of the non-saponifiable part of coffee-bean oil, and early attempts at purification (Noël and Dannmeyer, *Strahlentherapie*, 1929, **32**, 769; 1930, **38**, 583; Bengis and Anderson, *J. Biol. Chem.*, 1932, **97**, 99; Prescott, Emerson, Woodward, and Heggie, *Food Res.*, 1937, **2**, 165; Sabalitschka and Schüching, *Apoth. Ztg.*, 1938, **53**, 760; Wagner, *Z. Unters. Lebensm.*, 1939, **77**, 225; Slotta and Neisser, *Ber.*, 1938, **71**, 1991) were rendered difficult by presence of a more unsaturated substance known as kahweol, which was sensitive to oxygen, light, heat, and mineral acids and was responsible for the development of a yellow colour, the lowering in melting point, the increase in negative optical rotation on storage, and for the band in the ultraviolet spectrum at 2900 Å. The reported œstrogenic activity (Slotta and Neisser, *loc. cit.*) led to extensive structural investigations by the same authors (*Ber.*, 1938, **71**, 2342), Hauptmann and Franca (*Z. physiol Chem.*, 1939, **259**, 245; *J. Amer. Chem. Soc.*, 1943, **65**, 81), Wettstein, Fritzsche, Hunziker, and Miescher (*Helv. Chim. Acta*, 1941, **24**, 332 E), Wettstein and Miescher (*ibid.*, 1943, **26**, 631), Wettstein, Hunziker, and Miescher (*ibid.*, p. 1197), Wettstein, Spillmann, and Miescher (*ibid.*, 1945, **28**, 1004), Chakravorty, Levin, and Wesner (*J. Amer. Chem. Soc.*, 1943, **65**, 929), and Chakravorty, Levin, Wesner, and Reed (*ibid.*, p. 1325).

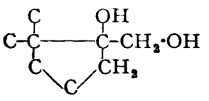
The early steroid structure suggested by Slotta and Neisser (*loc. cit.*, p. 2342) was abandoned when the œstrogenic inactivity of cafestol was established (Bauer and Neu, *Fette u. Seifen*, 1942, **49**, 419; Wettstein *et al.*, *loc. cit.*, 1941; Hauptmann and Franca, *loc. cit.*), and a structure of diterpenoid type came into favour. Cafestol was shown to contain a primary and a tertiary hydroxyl group (Slotta and Neisser, *loc. cit.*), which Hauptmann and Franca (*loc. cit.*) showed were present in an α-glycol structure, $>C(OH)\cdot CH_2\cdot OH$, yielding the aldehyde $-CH\cdot CHO$ when cafestol or its acetate was distilled with zinc dust; the tertiary hydroxyl group could also be eliminated with boiling acetic anhydride. Hydrogenation, as well as oxidation with per-acids, indicated presence of two double bonds, which were conjugated as proved by formation of an adduct with maleic anhydride (Wettstein *et al.*, *loc. cit.*, 1941). Wettstein *et al.* also oxidised cafestol with lead tetra-acetate; the glycol groupings was attacked with the formation of epoxynorcafestadienone, $C_{19}H_{24}O_2$, which was shown to be a *cyclo*pentanone as oxidation of the ketone (epoxynorcafestanone-A), similarly derived from tetrahydrocafestol, with potassium hypoiodite gave a dicarboxylic acid, $C_{19}H_{28}O_5$, yielding an anhydride. As the dibasic acid contained one hindered carboxyl group (methyl ester resistant to hydrolysis) which is probably † tertiary, the glycol grouping in cafestol may be present as partial structure (I) or (II). Although earlier workers failed, by treatment with *m*-nitrobenzaldehyde, to provide evidence for the ketomethylene group in epoxynorcafestadienone, Djerassi, Wilfred, Visco, and Lemin (*J. Org. Chem.*, 1953, **18**, 1449), during the course of our experiments, have established this by condensation with ethyl formate to a hydroxymethylene-ketone. They also confirmed the presence of the five-membered ring by infrared measurements on epoxynorcafestadienone (band at 1742 cm.$^{-1}$).

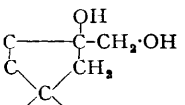
The nature of the third oxygen atom in cafestol has been the subject of several communications but contrary to earlier suggestions [Fieser and Fieser, " Natural Products

* A preliminary account of this work was published in *Chem. and Ind.*, 1954, 104.

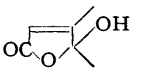
† But not of course conclusively so: the carboxyl group might also, for example, be secondary but subject to considerable steric hindrance. A similar ambiguity exists concerning one of the carboxyl groups formed in the oxidative fission of the six-membered ring adjacent to the furan ring (see p. 1984).

related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 80; Ferrari, *Il Farmaco* (*Pavia*), 1950, **5**, 47; 1951, **6**, 726; 1952, **7**, 3] the infrared spectrum shows absence of bands in the carbonyl region. Wettstein and Miescher (*loc. cit.*) put forward the concept of a 2 : 3-disubstituted furan ring (III) to explain the sensitivity to acids and the behaviour on oxidation and reduction. The furan ring is remote from the glycol grouping because Hauptmann and Franca (*loc. cit.*) showed by ultraviolet measurements that, when the tertiary hydroxyl group was removed by dehydration, the newly formed double bond is not conjugated with the original double bond system, and the carbonyl group of epoxynorcafestadienone is not in conjugation with the furan chromophore. Wettstein, Hunziker, and Miescher (*loc. cit.*) explained the reaction of per-acids with cafestol acetate on the basis of the conversion of the furan ring (III) into the hydroxy-lactone structure (IV). Again, the attachment of the furan ring to the remainder of the molecule was suggested by the


(I)


(II)


(III)

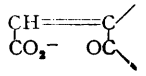

(IV)

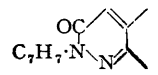
ozonisation of epoxynorcafestadienone to a keto-dicarboxylic acid, $C_{17}H_{24}O_5$, derived by rupture of the furan ring and loss of two mols. of carbon dioxide. This keto-dicarboxylic acid gave on pyrolysis a diketone, $C_{16}H_{22}O_2$, and consequently Wettstein, Hunziker, and Miescher (*loc. cit.*) deduced that the ring adjoining the furan ring was six- or seven-membered. It was also shown that the keto-dibasic acid probably contained one tertiary carboxyl group and that the diketone, $C_{16}H_{22}O_2$, condensed with *m*-nitrobenzaldehyde; in view of the failure of epoxynorcafestadienone to condense with *m*-nitrobenzaldehyde (see above) this evidence indicates presence of a ketomethylene group in the ring formed by pyrolysis of the keto-dicarboxylic acid, $C_{17}H_{24}O_5$. The oxidation of the maleic anhydride adduct of cafestol acetate to mellophanic acid suggested that the furan ring was attached to the rest of the molecule by the 2 : 3-carbon atoms. Djerassi and his co-workers (*loc. cit.*) have confirmed these views by measurements of the infrared spectrum of the diketone, $C_{16}H_{22}O_2$, which showed carbonyl bands at 1744 and 1737 cm.$^{-1}$ and consequently the presence of two *cyclo*pentanone rings.

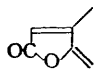
Our researches have overlapped to a certain extent with those of Djerassi and his co-workers, and our results confirm their findings. The isolation of pure cafestol from Santos coffee beans, Jamaica coffee beans, and coffee oil or residues kindly supplied by Messrs. J. Lyons and Company Limited is described in the Experimental section; we prefer partial hydrogenation for the elimination of kahweol from crude cafestol as this gives a product without the absorption band at 2900 Å, whereas it is evident from the ultraviolet data that the sodium and alcohol method used by Djerassi and his colleagues and by earlier workers is more tedious. Oxidation of cafestol to epoxynorcafestadienone was carried out with lead tetra-acetate as described by previous workers, and the ketone was readily reduced by hydrazine and potassium hydroxide in diethylene glycol to epoxynorcafestadiene. The new diene retained the furan ring and consequently gave a maleic anhydride adduct, and was reduced to a tetrahydro-derivative, epoxynorcafestane, by hydrogen in presence of palladium–charcoal. On ozonisation epoxynorcafestadiene gave a neutral product of unknown structure and a dibasic acid, $C_{15}H_{24}(CO_2H)_2$, m. p. 149—151°, which gave a cyclic ketone. The infrared spectrum of this ketone indicated a *cyclo*pentanone structure (band at 1740 cm.$^{-1}$) and consequently the dibasic acid was an adipic acid derived from a *cyclo*hexane precursor. These experiments therefore confirm that the ring attached to the furan nucleus is six-membered, and further evidence for this is presented below.

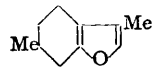
Monoperphthalic acid reacted with epoxynorcafestadiene to give hydroxynorcafestenolide, which contained partial structure (IV), the oxidation being analogous to the conversion of epoxynorcafestadienone into hydroxyoxonorcafestenolide, the acetyl derivative of which was described by Wettstein, Hunziker, and Miescher (*loc. cit.*). Partial structure (IV) has been supported by infrared and ultraviolet measurement, the latter in alkaline solution showing presence of the anion (V). Hydroxynorcafestenolide gave a crystalline

acetyl derivative, a cyclic compound of probable partial structure (VI) with *p*-tolylhydrazine, an anhydro-derivative (VII) when heated with potassium hydrogen sulphate, and the dibasic acid, $C_{15}H_{24}(CO_2H)_2$, m. p. 149—151°, on oxidation with permanganate. We have found that hydroxyoxonorcafestenolide may be prepared directly from cafestol by oxidation with chromic acid, a reagent which gives a similar result with menthofuran (VIII) (Wood-


(V)

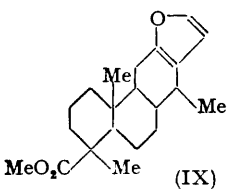

(VI)

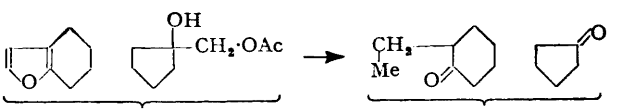

(VII)


(VIII)

ward and Eastman, *J. Amer. Chem. Soc.*, 1950, **72**, 399). The ketone was obtained in a crystalline form and gave an acetyl derivative, m. p. 235°, described previously by Wettstein, Hunziker, and Miescher (*loc. cit.*), and dehydration with potassium hydrogen sulphate gave an anhydro-derivative. Oxidation of epoxynorcafestadiene with chromic acid also gave hydroxynorcafestenolide and the above dibasic acid, m. p. 149—151°. The observation by Wettstein, Hunziker, and Miescher (*loc. cit.*) that cafestol acetate was oxidised by monoperphthalic acid, yielding (after further acetylation) diacetoxyhydroxycafestenolide, has been confirmed and we have hydrolysed the product to trihydroxycafestenolide.

In addition, the similarity of the infrared and ultraviolet absorption spectra of cafestol and its derivatives to those of authentic furans, particularly the 2 : 3-disubstituted methyl vinhaticoate (IX) (King and his co-workers, *J.*, 1953, 1055, 4158), leaves no doubt of presence of a furan ring in cafestol. Cafestol exhibits three bands in the infrared region characteristic of C=C stretching; these bands, at 1504 (strong), 1631 (weak), and 1563 cm.$^{-1}$ (very weak), are all absent from the spectrum of tetrahydrocafestol. Methyl vinhaticoate exhibits similar bands at 1506, 1638, and 1563 cm.$^{-1}$ which also disappear on hydrogenation of the furan ring. Differently substituted furans exhibit bands in the same region but not at identical positions: menthofuran (VIII) has strong bands at 1567 and 1642 cm.$^{-1}$ and a weak band at 1770 cm.$^{-1}$, whilst furfuryl alcohol absorbs at 1590 cm.$^{-1}$ (Rogers and Williams, *J. Amer. Chem. Soc.*, 1938, **60**, 2619) and furan at 1580 cm.$^{-1}$ (Pickett, *J. Phys. Chem.*, 1942, **10**, 660). The close similarity in ultraviolet absorption spectra of cafestol, menthofuran, and methyl vinhaticoate ($\lambda_{max.}$ 2220 Å in each case; log ε 3·80, 3·78, and 3·88 respectively) is also noteworthy.

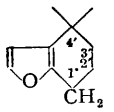

(IX)

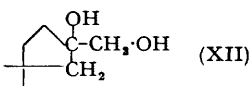

(X)

At an early stage in our experiments repeated unsuccessful attempts were made to prepare cafestol derivatives in which the furan ring had been opened by hydrogenolysis (cf. Wettstein, Fritzsche, Hunziker, and Miescher, *loc. cit.*), but as we could not improve the yields reported by the Swiss workers this approach was abandoned. Our results, which confirm and extend the earlier work, are reported in the Experimental section; it may be noted here that direct proof of hydrogenolysis was afforded by isolation of a triol diacetate, $C_{24}H_{38}O_5$, and additional evidence for presence of a six-membered ring adjoining the furan ring was provided by the infrared absorption spectrum of norcafestanedione (X), derived from cafestol acetate by hydrogenolysis, hydrolysis, and oxidation with chromic acid; the diketone (X) exhibited bands at 1740 (*cyclo*pentanone) and 1706 cm.$^{-1}$ (*cyclo*hexanone). The monoketone (epoxynorcafestanone A) derived from cafestol by hydrogenation of the furan ring and oxidative fission of the glycol group yielded a tribromo-derivative on exhaustive bromination, indicating presence of three hydrogen atoms in the α-position to the *cyclo*pentanone carbonyl group.

We believe the evidence now favours presence in cafestol of (1) the 2 : 3-disubstituted furan type (XI) and (2) the five-membered ring glycol of type (XII). The furan structure

(XI) is required to explain the following features. (*a*) At least one hydrogen atom must be present at 1′ to account for the formation of anhydro-derivatives of type (VII). (*b*) The

(XI) 

 (XII)

keto-dicarboxylic acid, $C_{17}H_{24}O_5$ (p. 1984), probably contains one tertiary carboxyl group, in which case no hydrogen atoms can be associated with 4′. (*c*) The diketone, $C_{16}H_{22}O_2$ (p. 1984), contains a ketomethylene group reactive to *m*-nitrobenzaldehyde, and two hydrogen atoms must therefore be present at 1′. The structure of type (XII) is necessary to explain (*a*) the conversion into epoxynorcafestadienone which contains a (hindered) ketomethylene group, (*b*) the probable tertiary nature of one carboxyl group in the dibasic acid, $C_{19}H_{28}O_5$ (p. 1983), and (*c*) the production of a tribromo-derivative from epoxynorcafestanone A (p. 1985).

On the other hand the hydrocarbon skeleton of cafestol is quite unknown and in spite of numerous experiments we have failed to isolate recognisable dehydrogenation products by the action of selenium on cafestol or the anhydro-lactones of type (VII); in fact an examination of the ultraviolet spectra of the oily products suggested that little aromatisation had been effected during reaction with selenium. Further attempted dehydrogenation experiments are in progress.

The analytical data for cafestol and its derivatives are, without exception, in agreement with $C_{20}H_{28}O_3$. This has been confirmed by a molecular-weight determination of acetoxynorcafestenolide ($C_{21}H_{28}O_4$) made for us by Dr. I. R. Beattie and Mr. O. S. Mills using the *X*-ray crystallographic method; their detailed findings will be published separately but their value of 343·8 $\pm$ 0·6 is in good agreement with value of 344·4 required for $C_{21}H_{28}O_4$ derived from a $C_{20}H_{28}O_3$ formula for cafestol. Therefore in addition to the furan ring cafestol must contain either four carbocyclic rings or, as discussed by Djerassi and his coworkers (*loc. cit.*), it has an unreactive double bond and three carbocyclic rings as frequently found in other diterpenes. The former arrangement is preferable as we find that tetrahydrocafestol acetate is almost transparent throughout the whole measurable range of the ultraviolet absorption spectrum; the extinction of 2120 Å is of the same order as that of cholestan-3β-yl acetate, and consequently the existence of an unreactive double bond in the molecule must be excluded. The stability of epoxynorcafestanone A to vigorous treatment with hydrogen chloride or sulphuric acid, and the absence of bands at 1000—1020 cm.$^{-1}$ from the infrared spectrum of this compound or of cafestol, appear to exclude presence of a *cyclo*propane ring; it may also be noted that neither of the two compounds last named exhibits a band at 3042—3052 cm.$^{-1}$ which would correspond to a *cyclo*propane methylene group. A similar search for a *cyclo*butane ring has not been made.

The additional ultraviolet chromophore at 2900 Å present in kahweol is no doubt (as suggested by Djerassi *et al.*) due to the presence of a homoannular diene system (cf. Fieser and Fieser, *op. cit.*, p. 185) and, although very little is known about the structure of this product, it may be noted that the additional chromophore does not conjugate either with the furan ring or with the *cyclo*pentanone carbonyl group formed by oxidative elimination of the glycol side chain. Nevertheless some kind of loose interaction between the furan ring and the additional chromophore in kahweol is indicated by the progressive reduction in extinction at 2220 Å in samples of crude cafestol (or derivatives) containing increasing amounts of kahweol (or derivatives) as indicated, *inter alia*, by progressive increase in extinction at 2900 Å.

Experimental

Optical rotatory values were determined in $CHCl_3$ and ultraviolet absorption spectra were measured in EtOH.

Isolation of Cafestol.—A modification of Slotta and Neisser's method (*loc. cit.*) was used. Ground coffee beans (900 g.) which had been dried at 100° for 24 hr. were mixed with chloroform (1 l.) and shaken occasionally during 72 hr. Filtration and removal of the solvent gave a brown oil (110 g.), which was mixed with light petroleum (b. p. 40—60°; 200 c.c.) and left overnight at

0°. The precipitated caffeine was collected and the residual oil (100 g.) was introduced into well-stirred 10% aqueous sodium hydroxide (125 c.c.), and stirring continued for 3 hr. Ethanol (100 c.c.) was added, and stirring continued for a further 3 hr. Water (250 c.c.) and ethanol (90 c.c.) were added and the mixture was stirred until an almost clear solution was obtained. The solution was then continuously extracted with ether for 18 hr., and the extract, after being washed with water and dried, gave a pale brown oil which, on addition of light petroleum (b. p. 40—60°; 50 c.c.), yielded a pale yellow solid. The solid was extracted in a Soxhlet apparatus with light petroleum (b. p. 60—80°) and recovered as an almost colourless solid which was twice crystallised from light petroleum (b. p. 60—80°). The results are summarised in the Table.

Source	Yield (g.)	M. p.	$[\alpha]_D$	$\log \varepsilon_{2220}$	$\log \varepsilon_{2900}$
Dried green Santos Bourbon coffee beans	3·9	150—154°	−138° ± 3°	3·75	3·45
Coffee oil (Messrs. J. Lyons)	1·9 from 220 g. of oil	148—153	−122° ± 2°	3·76	3·10
Jamaica coffee beans	5·5	150—153	—	3·63	3·76

An attempt to utilise roasted coffee grounds from which water-soluble materials had been removed by Messrs. J. Lyons & Company Limited was not profitable because of difficulties in purification, and the poor yields of cafestol.

Purification of Cafestol.—(*a*) Crude cafestol [500 mg.; $\lambda_{max.}$ 2900 Å (log ε 3·49)] with acetic anhydride (1 c.c.) in pyridine (3·3 c.c.) gave an acetate crystallising from light petroleum (b. p. 60—80°) in needles, m. p. 159—160°, $[\alpha]_D$ −133° ± 3°, $\lambda_{max.}$ 2220 Å (log ε 3·72), 2900 Å (log ε 3·46), which gave a maleic anhydride adduct, m. p. 187—189° (decomp.) (from acetone). The acetate (400 mg.) in ethanol (20 c.c.) was shaken with hydrogen in presence of 2% palladium–charcoal (70 mg.), and after the rapid uptake (10 c.c.) ceased, pure cafestol acetate separated from light petroleum (b. p. 60—80°) in needles (360 mg.), m. p. 167—168°, $[\alpha]_D$ −89° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å (Found: C, 73·7; H, 8·7. Calc. for $C_{22}H_{30}O_4$: C, 73·7; H, 8·4%). The maleic anhydride adduct separated from acetone in cubes, m. p. 195—196° (Found: C, 68·6; H, 7·2. Calc. for $C_{26}H_{32}O_7$: C, 68·4; H, 7·0%), from which cafestol acetate, m. p. 165—167°, was recovered by refluxing with phellandrene in benzene for 20 hr. Pure cafestol acetate (500 mg.), refluxed for 3 hr. with potassium carbonate (2 g.), methanol (15 c.c.), and water (10 c.c.), gave cafestol (390 mg.), m. p. 158—159°, $[\alpha]_D$ −101° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·78), no band at 2900 Å.

(*b*) Crude cafestol [7 g.; $\lambda_{max.}$ 2900 Å (log ε 3·49)] absorbed hydrogen (161 c.c.) during 30 min., in ethanol in presence of 2% palladium–charcoal, and yielded a product, m. p. 157—159°, $[\alpha]_D$ −103° ± 2°, $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å (Found: C, 76·1; H, 8·9%; *C*-Me, 1·1. Calc. for $C_{20}H_{28}O_3$: C, 75·9; H, 8·9%). Pure cafestol gave, in benzene, a maleic anhydride adduct which crystallised from acetone in colourless needles, m. p. 191—193°.

Cafestol, prepared by method (*a*) or (*b*), did not alter in appearance after several weeks; crude cafestol, m. p. 150—154°, and containing kahweol became yellow and had m. p. 110—145° after a similar period.

Epoxynorcafestadiene.—Cafestol (1 g.), oxidised with lead tetra-acetate as described by Wettstein, Fritzsche, Hunziker, and Miescher (*loc. cit.*), yielded epoxynorcafestadienone, which crystallised from ether–light petroleum (b. p. 40—60°) in colourless needles (650 mg.), m. p. 176—178° (Found: C, 79·9; H, 8·5. Calc. for $C_{19}H_{24}O_2$: C, 80·2; H, 8·5%), $\lambda_{max.}$ 2220 Å (log ε 3·80). The infrared spectrum exhibited a band at 1740 cm.$^{-1}$. A *C*-methyl determination gave 1·1 methyl groups. The semicarbazone separated from methanol in colourless needles, m. p. 244—245° (decomp.) (Found: C, 70·0; H, 7·8; N, 12·6. Calc. for $C_{20}H_{27}O_2N_3$: C, 70·4; H, 8·0; N, 12·3%). Epoxynorcafestadienone (300 mg.) in diethylene glycol (10 c.c.) containing hydrazine hydrate (90%; 300 mg.) was refluxed for 0·5 hr.; potassium hydroxide (2 g.) was added and refluxing continued for a further hour; after concentration to b. p. 190°, the solution was refluxed for a further 3 hr. and poured into water (100 c.c.); the product, isolated by continuous ether-extraction, was a pale brown oil which solidified after distillation at 160° (bath)/0·1 mm. *Epoxynorcafestadiene* separated from alcohol in colourless needles (190 mg.), m. p. 93—94° (Found: C, 84·6; H, 9·4. $C_{19}H_{26}O$ requires C, 84·4; H, 9·7%), $\lambda_{max.}$ 2220 Å (log ε 3·80), no band at 2900 Å. The maleic anhydride *adduct*, prepared in cold benzene, crystallised from acetone in colourless needles, m. p. 181—182° (Found: C, 74·7; H, 7·6. $C_{23}H_{28}O_4$ requires C, 75·0; H, 7·6%).

Epoxynorcafestane.—Epoxynorcafestadiene (170 mg.) in acetic acid (20 c.c.) was hydrogenated in presence of 10% palladium–charcoal (10 mg.). After the uptake of 2 mols. of hydrogen and removal of the catalyst, the solution was diluted with water and the *product*, isolated with

ether, crystallised from aqueous methanol in colourless needles (150 mg.), m. p. 62—63° (Found : C, 82·8; H, 11·0. $C_{19}H_{30}O$ requires C, 83·2; H, 11·0%).

Ozonolysis of Epoxynorcafestadiene.—A stream of oxygen containing 2% of ozone was passed through epoxynorcafestadiene (490 mg.) in ethyl acetate (15 c.c.) cooled in acetone–carbon dioxide, until three times the calculated amount for the saturation of one double bond had been introduced. The solvent was removed under reduced pressure, the ozonide was decomposed on the steam-bath with water (10 c.c.) containing hydrogen peroxide (100-vol.; 0·4 c.c.) for 1 hr., and the products were taken up in chloroform and separated by dilute sodium hydroxide solution into neutral and acidic fractions. The neutral fraction (50 mg.) was distilled at 160° (bath)/0·1 mm., and the distillate crystallised from ether–light petroleum (b. p. 40—60°); colourless needles, m. p. 190—192° (decomp.) (Found : C, 71·1, 71·6; H, 8·0, 8·1%), were obtained which exhibited a strong band at 1737 $cm.^{-1}$ (CO). The acidic fraction (450 mg.) was distilled at 170° (bath)/0·1 mm. and yielded a glass which separated from ether–light petroleum (b. p. 40—60°) in colourless needles, m. p. 149—151° [Found : equiv., 151; C, 69·3; H, 8·7%. $C_{15}H_{24}(CO_2H)_2$ requires equiv., 147; C, 69·4; H, 8·9%], showing strong bands at 1704 and 3330 $cm.^{-1}$.

The Ketone, m. p. 126—128°.—The above dibasic acid (300 mg.) was refluxed with excess of acetic anhydride for 4 hr. and the whole set aside overnight. The mixture was poured into water and extracted with ether. The extract, washed with sodium hydrogen carbonate solution and water, gave an oil which was heated for 4 hr. at 180°/20 mm. and then distilled at 170° (bath)/0·1 mm.; a colourless oily *ketone* (130 mg.) was obtained which crystallised from methanol in irregular prisms, m. p. 126—128° [Found (on small quantity of material) : C, 81·8; H, 10·2. $C_{16}H_{24}O$ requires C, 82·7; H, 10·4%], exhibiting a band at 1740 $cm.^{-1}$ (CO).

Oxidation of Cafestol with Chromium Trioxide.—Chromium trioxide (3·6 g.) in acetic acid (80 c.c.) and water (4 c.c.) was added to cafestol (1 g.) in acetic acid (10 c.c.). After 24 hr. methanol (6 c.c.) was added and after another hour the mixture was diluted with water, and the products were isolated by continuous ether-extraction. The extract, washed with sodium hydrogen carbonate solution, yielded hydroxyoxonorcafestenolide (300 mg.) which crystallised from acetone in colourless needles, m. p. 253—254° (Found : C, 72·0; H, 7·4. Calc. for $C_{19}H_{24}O_4$: C, 72·1; H, 7·6%). The acetyl derivative, prepared with acetic anhydride in pyridine, had m. p. 235—236° (Found : C, 69·8; H, 7·3. Calc. for $C_{21}H_{26}O_5$: C, 70·4; H, 7·3%). The hydroxyoxonorcafestenolide and its acetyl derivative were apparently identical with the compounds prepared as described by Wettstein, Hunziker, and Miescher (*loc. cit.*).

Dehydration of Hydroxyoxonorcafestenolide.—The hydroxy-ketone (50 mg.) was mixed with a small amount of sodium hydrogen sulphate and distilled at 200° (bath)/0·1 mm. The distillate was sublimed at 160° (bath)/0·1 mm. and crystallised several times from alcohol; the *anhydro-derivative* was obtained as needles (30 mg.), m. p. 232—234° (Found : C, 76·0; H, 7·5. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%), which gave hydroxyoxonorcafestenolide in warm methanolic sodium hydroxide. Light absorption : $\lambda_{max.}$ 2750 Å (log ε 4·16).

Hydroxycafestenolide and its Derivatives.—Ethereal monoperphthalic acid (70 c.c., containing 2·02 g. of acid) was added to epoxynorcafestadiene (1 g.); the latter rapidly dissolved and the solution was kept at 0° for 60 hr., 2·0 equivs. of per-acid being utilised. The solvent was removed under reduced pressure and the residue, extracted four times with benzene–chloroform (1·1 mixture), gave an oil (no colour with tetranitromethane). The oil was acetylated with acetic anhydride (10 c.c.) and pyridine (15 c.c.); after 24 hr. the mixture was diluted with water, and *acetoxynorcafestenolide*, isolated with ether and purified by passage through a column of alumina, crystallised from acetone–light petroleum (b. p. 60—80°) in large cubes (600 mg., m. p. 173—175° (Found : C, 73·1; H, 7·8. $C_{21}H_{28}O_4$ requires C, 73·2; H, 8·2%).

Hydrolysis with potassium carbonate (5 parts), methanol (70 vols.), and water (30 vols.) gave *hydroxynorcafestenolide* which crystallised from ether–light petroleum (b. p. 40–60°) in needles, m. p. 196—197° (Found : C, 75·1; H, 8·5. $C_{19}H_{26}O_3$ requires C, 75·4; H, 8·7%).

When heated for 24 hr. with *p*-tolylhydrazine hydrochloride (80 mg.) and sodium acetate (90 mg.) in aqueous methanol (90%; 5 c.c.) hydroxynorcafestenolide (50 mg.) gave a *derivative* which crystallised from ether–light petroleum (b. p. 40—60°) in yellow needles (30 mg.), m. p. 226—228° (Found : C, 80·0; H, 8·2; N, 7·3. $C_{26}H_{32}ON_2$ requires C, 80·4; H, 8·3; N, 7·2%). The *anhydro-derivative* sublimed when a mixture of hydroxynorcafestenolide and sodium hydrogen sulphate was heated at 160° (bath)/0·1 mm.; crystallisation from alcohol gave needles, m. p. 158—159° (Found : C, 80·7; H, 8·5. $C_{19}H_{24}O_2$ requires C, 80·3; H, 8·5%), $\lambda_{max.}$ 2750 Å (log ε 4·17).

Chloroacetoxynorcafestenolide.—Hydroxynorcafestenolide (200 mg.) was treated in benzene

(15 c.c.) with chloroacetyl chloride (3 c.c.) and dimethylaniline (1 c.c.). After 48 hr. at 20° the mixture was shaken successively with dilute hydrochloric acid and water, and the dried benzene layer evaporated. The residue was taken up in benzene–light petroleum (b. p. 40—60°) (1 : 2) and absorbed on an alumina column, and the fraction (110 mg.) eluted with benzene–light petroleum (b. p. 40—60°) (100 c.c.; 1 : 1) crystallised from ether–light petroleum (b. p. 40—60°) in colourless plates (70 mg.), m. p. 150—151° (Found : C, 66·5; H, 6·9. $C_{21}H_{27}O_4Cl$ requires C, 66·6; H, 7·2%).

Oxidation of Epoxynorcafestadiene with Chromium Trioxide.—Epoxynorcafestadiene (1 g.) in acetic acid (10 c.c.) was oxidised at room temperature with chromium trioxide (3·5 g.) in acetic acid (70 c.c.) and water (5 c.c.). After 24 hr. the products were separated (bicarbonate) into neutral and acidic fractions. The neutral fraction, on chromatography from acetone on alumina and crystallisation from ether–light petroleum (b. p. 40—60°), gave hydroxynorcafestenolide (350 mg.), m. p. 196—197°. The acidic fraction (250 mg.) was distilled at 170° (bath)/0·1 mm., and the product separated from ether–light petroleum (b. p. 40—60°) in needles (150 mg.), m. p. 149—151°, identical with the dibasic acid obtained (*a*) by ozonolysis of epoxynorcafestadiene (p. 1988) and (*b*) by oxidising hydroxynorcafestenolide with alkaline potassium permanganate at room temperature for 12 hr.

Hydrolysis of Diacetoxyhydroxycafestenolide.—Diacetoxyhydroxycafestenolide (200 mg.), prepared from cafestol acetate as described by Wettstein, Hunziker, and Miescher (*loc. cit.*), was refluxed for 3 hr. with potassium carbonate (800 mg.) in aqueous methanol (70%; 20 c.c.). The solution was diluted with water, neutral products were removed in chloroform and ether, and the aqueous layer was acidified and extracted first with chloroform and then with ether. Evaporation of the dried combined extracts gave trihydroxycafestenolide which crystallised from acetone–light petroleum (b. p. 40—60°) in colourless needles, m. p. 234—236° (Found : C, 68·4; H, 8·3. $C_{20}H_{28}O_5$ requires C, 68·9; H, 8·1%).

Hydrogenation of Cafestol and its Derivatives.—Many hydrogenations were carried out on cafestol or its acetate with palladium, platinum oxide, and Raney nickel catalysts. Hydrogenation of cafestol in presence of 10% palladium–charcoal gave epoxycafestanediol, m. p. 156—157° (acetate, m. p. 152—154°, ε_{2120} 95), oxidised by lead tetra-acetate to epoxynorcafestanone A, m. p. 129—130°, ε_{2070} 197. The m. p.s of these compounds correspond with those given by Wettstein, Hunziker, and Miescher (*loc. cit.*). *Epoxynorcafestanone oxime* separated from dilute methanol in colourless needles, m. p. 192—194° (Found : N, 4·3. $C_{19}H_{29}O_2N$ requires N, 4·6%). The ketone (50 mg.) in acetic acid (15 c.c.) containing bromine (150 mg.) was kept for 24 hr. in the dark at room temperature; the *tribromo-derivative* separated from dilute acetic acid in nodules, m. p. 110—114° (Found : C, 43·5; H, 4·4; Br, 45·3. $C_{19}H_{25}O_2Br_3$ requires C, 43·5; H, 4·8; Br, 45·6%).

Reduction of cafestol acetate (1·06 g.) in acetic acid (40 c.c.) in presence of platinic oxide (0·28 g.) at room temperature and pressure resulted in the uptake of 2·5 mols. of hydrogen. Chromatography of the product on alumina (25 g.) gave a heterogeneous fraction (90%) on elution with benzene and ether, but elution with acetone gave a fraction (10%), m. p. 179—180°. The latter fraction (hydrogenolysis product) gave a *diacetyl derivative* which crystallised from light petroleum (b. p. 40—60°) in colourless nodules, m. p. 81° (Found : C, 70·7; H, 9·1. $C_{24}H_{38}O_5$ requires C, 70·9; H, 9·3%). Hydrolysis of the earlier fractions (monoacetates) and oxidation with chromium trioxide in acetic acid yielded a mixture apparently of epoxynorcafestanone A, m. p. 131—132°, and epoxynorcafestanone B, m. p. 165—166°; these ketones, with the same m. p.s, were obtained by Wettstein, Fritzsche, Hunziker, and Miescher (*loc. cit.*) from cafestol acetate by hydrogenation, hydrolysis, and oxidation with periodic acid.

Methyl Tetrahydrovinhaticoate.—Our thanks are offered to Professor F. E. King, F.R.S., for a generous gift of methyl vinhaticoate which was hydrogenated as described by King, King, and Neill (*J.*, 1953, 1055); the *product* separated from methanol in colourless needles, m. p. 90—91° (Found : C, 74·9; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·3%).

Our thanks are offered to British Schering Limited and to Drs. E. B. Hughes and L. H. Lampitt of Messrs. J. Lyons & Company Limited for gifts of cafestol, coffee-bean oil, and coffee grounds, to Dr. G. D. Meakins of Manchester University and Imperial Chemical Industries Limited, Billingham Division, for some of the infrared measurements, to Imperial Chemical Industries Limited for a grant towards the expenses of this research, and to the Department of Scientific and Industrial Research for a maintenance allowance to one of us (A. H. J.).

THE UNIVERSITY, SHEFFIELD. [*Received, February 16th*, 1955.]