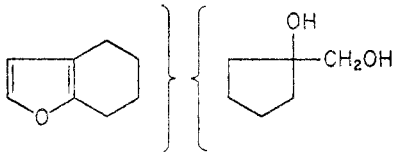
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

TERPENOIDS. XIX.[1] THE PENTACYCLIC SKELETON OF CAFESTOL

CARL DJERASSI, HILLEL BENDAS[2], AND PASUPATI SENGUPTA[3]

Received April 8, 1955

In our first communication (1) on cafestol ($C_{20}H_{28}O_3$), an important constituent of the non-saponifiable portion of coffee oil, there was given a complete literature survey complemented by our own spectroscopic results. On the basis of these data, it was concluded that the partial formulation (I), namely a furan ring fused to a six-membered carbocyclic ring as well as the attachment of a glycol grouping to a cyclopentane ring, as suggested originally by Wettstein, Hunziker, and Miescher (2) was indeed justified. It was also pointed out that unless cafestol possessed a hindered and hitherto undetected double bond, it must be pentacyclic in which case the nature of two carbocyclic rings was still unknown. Recently, Haworth, Jubb, and McKenna (3) observed that tetrahydrocafestol, in which the furan ring had been reduced, was completely transparent throughout the entire ultraviolet region which suggested the absence of an additional double bond (4).



I

The obvious approach to the elucidation of the skeleton of cafestol would involve dehydrogenation, which has proved to be so useful in structure studies in the steroid and terpene series. Such dehydrogenations of cafestol, however, have met with conspicuous failure (3, 5) and we have, therefore, undertaken a systematic study of the dehydrogenation of various degradation products of cafestol. The results, to be described below, provide the first chemical proof for the pentacyclic nature of cafestol and also demonstrate the presence of a perhydro-phenanthrene skeleton in this substance.

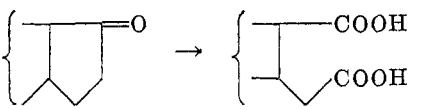
King and King (6) in their investigation of the diterpene methyl vinhaticoate, have shown that dehydrogenation of furanoperhydrophenanthrenes can lead to phenanthrols, which has the marked advantage of "labeling" the point of attachment of the furan ring. This proved to be the method of choice since it led for the first time to the isolation of crystalline dehydrogenation products in the cafestol series. Lead tetraacetate cleavage (7) of the glycol grouping of

[1] Paper XVIII, Walter, Bickoff, Thompson, Robinson, and Djerassi, *J. Am. Chem. Soc.*, in press.

[2] General Foods Corporation Postdoctorate Research Fellow, 1954–1955.

[3] General Foods Corporation Postdoctorate Research Fellow, 1953–1954.

cafestol produces the derived ketone, epoxynorcafestadienone, which has been shown (1, 7) to be part of a five-membered ring. Wolff-Kishner reduction gave epoxynorcafestadiene, in which the furan ring was still intact, but this substance proved unsuitable since no crystalline dehydrogenation products were encountered. Wettstein and co-workers (7) have shown in the *tetrahydro* series (furan ring reduced) that hypoiodide oxidation of the ketone (IIa) transforms it to a dibasic acid (IIIa) in which one of the carboxyl groups was very hindered. We have now applied the same oxidation to epoxynorcafestadienone (IIb) and have obtained the corresponding dibasic acid (IIIb), further characterized as the dimethyl ester. This seemed to be the ideal substrate for dehydrogenation studies since except for rupture of the cyclopentane ring, it still contains the intact cafestol skeleton and in particular the two, hitherto undefined carbocyclic rings.



II III

(a) with tetrahydrofuran ring
(b) with furan ring

Dehydrogenation with a palladium catalyst led to a complex mixture which was separated into neutral and phenolic fractions. The neutral fraction, which crystallized readily, so far has not been resolved into its pure components, but the ultraviolet absorption spectrum was typical of a phenanthrene hydrocarbon. Of even greater importance was the phenolic fraction, because the remaining oxygen atom must have been that of the furan ring which was ruptured during the dehydrogenation. In one instance, when the dehydrogenation was carried out at 360–400°, a small amount of a phenol (m.p. 165°) was isolated, the ultraviolet absorption spectrum (Fig. 1) of which was superimposable with that of authentic 2-phenanthrol (m.p. 173°). A mixture melting point was not depressed and the x-ray diffraction patterns of the two samples were very similar. Nevertheless, it cannot be stated with absolute certainty whether the dehydrogenation product is 2-phenanthrol, its lower melting point being due to an impurity, or whether it is x-methyl-2-phenanthrol since the analytical results will not differentiate between these two possibilities. However, the important fact, to be deduced from this experiment, is that cafestol must contain a *perhydrophenanthrene skeleton with the furan oxygen atom attached to position 2*, since the ultraviolet absorption spectra of the various phenanthrols (Fig. 1) differ in a very characteristic manner.

When the dehydrogenation was carried out at a lower temperature, another phenol (m.p. 152°) was isolated. It again showed a typical phenanthrene spectrum (Fig. 1), similar to that of 2-phenanthrol but all of the maxima were shifted slightly to higher wave length. The analytical results of this phenanthrol and its 3,5-dinitrobenzoate do not differentiate between the empirical formulas $C_{16}H_{14}O$ (ethylphenanthrol) or $C_{17}H_{16}O$ (ethylmethylphenanthrol). It is clear, that the ethyl group, which survived in this dehydrogenation, resulted from the opening of the furan ring, leaving only two positions (1 or 3) open for con-

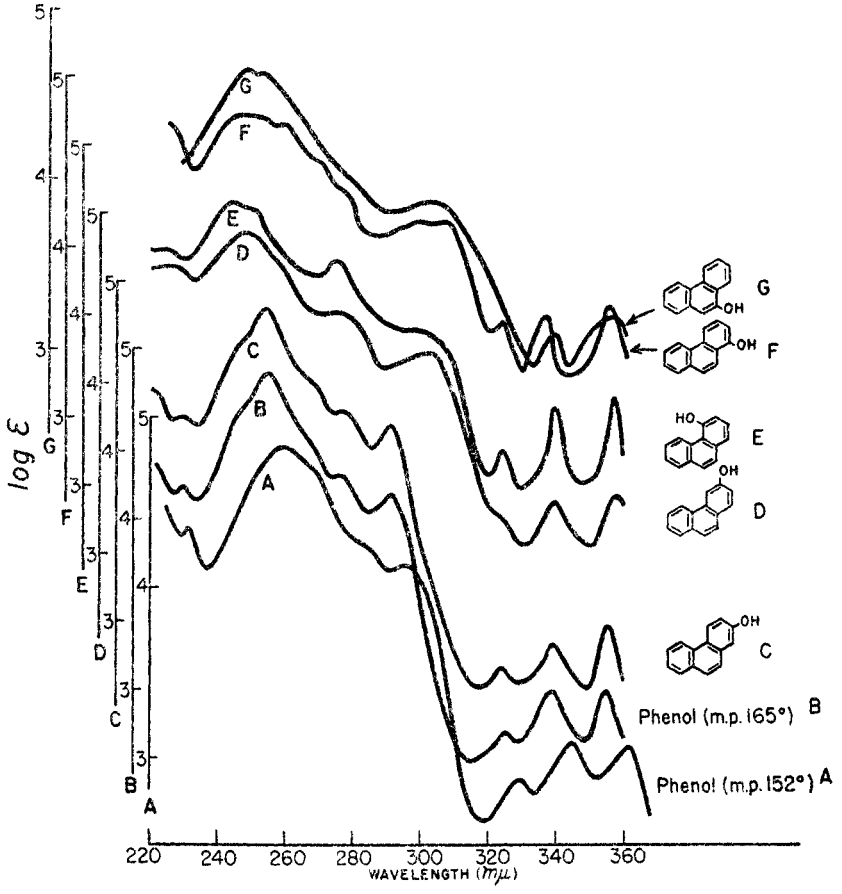
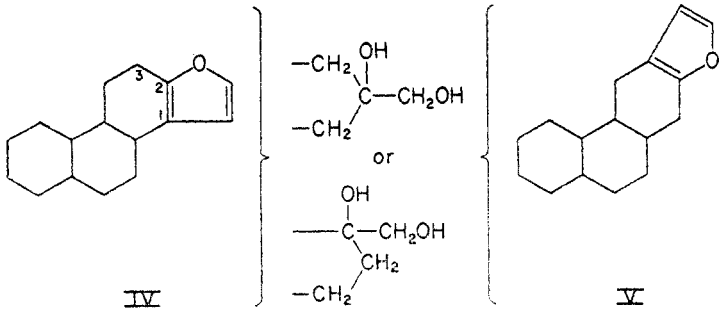


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN ABSOLUTE ALCOHOL SOLUTION

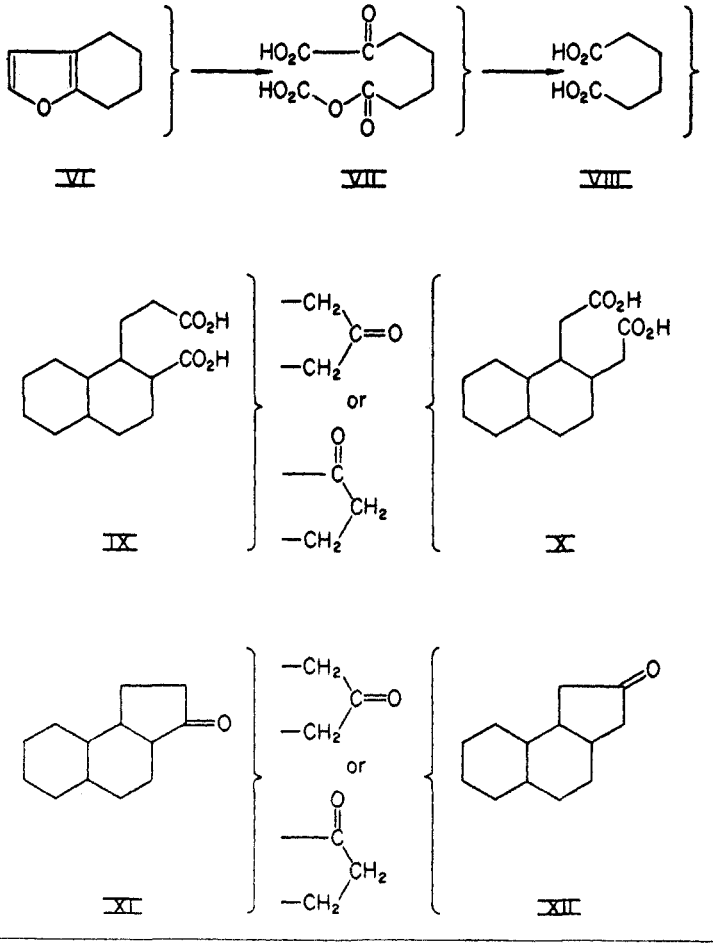
sideration. This would lead to partial structures IV or V for cafestol, the attachment of the cyclopentane ring being undecided.



IV V

A decision between IV and V can be made with a fair degree of certainty on the basis of previously reported (1, 2) degradations of epoxynorcafestadienone, in which the six-membered nature of the ring (partial structure VI) to which

the furan ring is attached was established. Ozonization and oxidative decomposition of the ozonide, presumably proceeding *via* VII furnished a dicarboxylic acid (VIII), in which one of the carboxyl groups is hindered (2). Using the two partial structures IV and V, the dicarboxylic acid (VIII) would now become either IX or X and only in the former[4] would a differential reactivity of the two carboxyl groups be expected. Pyrolysis (1, 2) of the dicarboxylic acid (IX or X) leads to a diketone (XI or XII), both carbonyl groups being present as cyclopentanones (1). The methylene group adjacent to the original carbonyl function of epoxynorcafestadienone is hindered since it will not condense with aromatic aldehydes (7) but does form (1) a hydroxymethylene derivative. We have now observed that the more reactive[5] furfural similarly fails to condense with epoxynorcafestadienone and that the diketone (XI or XII) forms only a

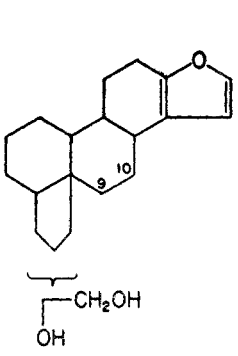


[4] This argument would not be valid if cafestol possessed a structure in which the cyclopentane ring is attached to positions 4 and 4a.

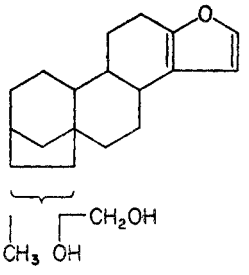
[5] We are greatly indebted to Drs. W. S. Johnson and R. Pappo of the University of Wisconsin for the condensation procedure.

mono-furfurylidene derivative[6] indicating that the newly produced cyclopentanone contains only one reactive α-methylene group. All of these observations are most compatible[4] with partial structures IV (cafestol), IX (dicarboxylic acid), and XI (diketone).

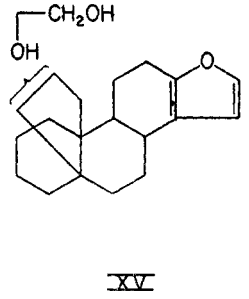
In order to arrive at a complete expression for cafestol, it is now only necessary to attach the cyclopentane ring bearing the glycol grouping to partial structure IV. In principle, this can be done in two ways which are illustrated by structures XIII or XIV, the points of attachment being chosen arbitrarily. The first structure (XIII) already contains all of the carbon atoms of cafestol while in XIV, it would be necessary to place at some point a methyl group. Kuhn-Roth oxidations, carried out in four different analytical laboratories, on cafestol, epoxynorcafestadienone, and the dicarboxylic acid (*e.g.* XX) failed to offer an unequivocal answer since the C-methyl values were very low. Consequently, structures of type XIV cannot be ignored at the present time and experiments are under way by which a direct chemical differentiation should be possible between a cyclopentane ring fused to the 1,3 (*e.g.* XIV) as compared to the 1,2-positions (*e.g.* XIII, XV) of one of the cyclohexane rings.



XIII



XIV



XV

Ring opening of epoxynorcafestadienone, the lead tetraacetate oxidation product of cafestol, leads to a dibasic acid (7, 8) in which one of the carboxyl groups is extremely hindered and which most likely is attached to a quaternary carbon atom. Hence the cyclopentane ring must originate at least at one of the angular positions, two typical examples being illustrated by XIII and XIV. It should be noted that in each instance two of the possible structures (five-membered ring terminating at C-9 or C-10) can probably be disproved readily by determining whether a suitable phenanthrene dehydrogenation product yields a 9,10-quinone. The present results are equally compatible with structures in which the cyclopentane ring terminates in two angular positions and XV illustrates one of three[7] such theoretical possibilities.

[6] The formation of a mono-*m*-nitrobenzylidene derivative has already been recorded (ref. 2).

[7] This does not take into account possible stereochemical restrictions.

There remains for consideration one last aspect, namely the point of attachment of the glycol grouping to the five-membered ring. Employing XIII as an example, there exist three alternatives which are illustrated by partial structures XVI, XVII, and XVIII for the derived epoxynorcafestadienone. Of these, XVI (or its equivalent depending upon the exact termination points of the cyclopentane ring) would appear unlikely[8] since the dibasic acid XIX, arising by oxidative opening would not be expected to possess as hindered a carboxyl group as had been observed experimentally (7, 8). Both XVII and XVIII could give rise to the same dibasic acid (XI) which would be of the type to be expected on the basic of the experimental results.

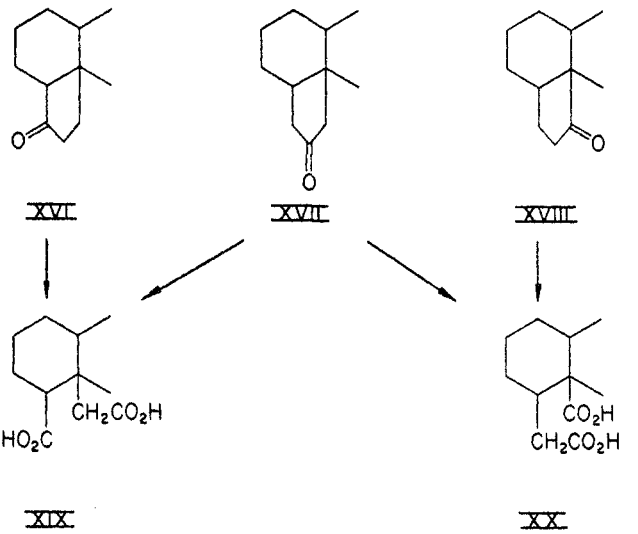
A tentative choice between a structure of type XVII, in which the carbonyl group is flanked by two methylene groups, and XVI or XVIII, in which only one α-methylene group is present, can be made by means of the Zimmermann color reaction. It has been called to our attention by Dr. David K. Fukushima (Sloan-Kettering Institute for Cancer Research) that a ketone of type XVIII should give a true magenta color in the Zimmermann reaction, as shown by 17-ketosteroids, while XVII would give a brown color as exhibited by 3- or 16-ketosteroids which possess two α-methylene groups. When epoxynorcafestadienone was examined under those conditions[9] it gave a typical magenta color but only of *ca.* one-fifth the intensity when compared in a parallel run with a standard 17-ketosteroid. The reduced intensity is probably a reflection of the more hindered character of the adjacent methylene group as has actually been demonstrated experimentally with epoxynorcafestadienone (1, 2, 8). While the results of the Zimmermann reaction would not be of any help in deciding the point of attachment of the glycol grouping in structures exemplified by XIV, the two other structural alternatives for cafestol represented by XIII or XV can be narrowed down to those expressions in which the glycol grouping is attached to one of the carbon atoms joined directly to the phenanthrene nucleus. In the case of XIII, an additional limitation is imposed by the above expressed preference of the derived dibasic acid formulation XX over XIX which leads to structure XVIII (or its equivalent depending upon the actual attachment of the cyclopentane ring) as a possible representation for epoxynorcafestadienone.

It should be noted that if the dibasic acid used in our dehydrogenation studies possesses structure XX (or a positional isomer), then the phenol (m.p. 152°) isolated in the dehydrogenation is most likely x-methyl-1-ethyl-2-phenanthrol. On the other hand, if XIV or XV (or their equivalents) represent the mode of

[8] A structure of type XVI could not be differentiated at this time from XVIII if the cyclopentane ring terminated in two angular positions (*cf.* XV), while in a cafestol structure based on XIV or its equivalent the same dibasic acid would be obtained irrespective of the location of the glycol grouping.

[9] We are grateful to Dr. Fukushima for carrying out this color reaction *quantitatively* according to the Callow modification of the Zimmermann reaction (Callow, Callow, and Emmens, *Biochem. J.*, **32**, 1312 (1938)), 1.427 mg. of epoxynorcafestadienone being equivalent to 0.32 mg. of dehydroepiandrosterone. Wettstein and Miescher (8) encountered erratic (*qualitative*) results with the Zimmermann reaction, epoxynorcafestadienone giving a negative reaction and its tetrahydroanalog (IIa) a faint violet color.

attachment of the cyclopentane ring in cafestol, then the product should be 1-ethyl-2-phenanthrol. Synthetic experiments are now in progress in order to differentiate between these alternatives.[9a]



XVI XVII XVIII XIX XX

All of the cafestol employed in this as well as in earlier work by other groups (*cf.* ref. 1) contained appreciable amounts of an unsaturated companion substance, kahweol, which was usually removed by sodium-alcohol reduction, although partial hydrogenation (3) has recently been recommended. The question may arise whether these cafestol samples are identical with the naturally occurring material or whether an alteration was introduced by the chemical purification methods. In connection with our cafestol work, we have examined a considerable number of coffee oil samples from various sources and while these results will not be considered at this time, it is pertinent to mention that from African coffee oil, we have isolated cafestol which was essentially free of kahweol and which in its properties was undistinguishable from chemically purified cafestol specimens obtained from Santos or other American coffee oils. Consequently, the chemical purification procedures do not appear to affect cafestol to any extent.

EXPERIMENTAL[10]

Epoxynorcafestadiene. A solution of 1.0 g. of epoxynorcafestadienone (1, 7), 80 cc. of diethylene glycol, and 6.8 cc. of hydrazine hydrate was refluxed for 30 minutes, 1 g. of potassium hydroxide was added, and refluxing was continued for 1 hour. The condenser was removed and the mixture was heated until the temperature rose to 190° at which point

[9a] Note added in proof: The phenol has now been identified as 1-ethyl-2-phenanthrol by an independent synthesis. Consequently structures of type XIV or XV are to be preferred for cafestol.

[10] Melting points were determined on the Kofler block. Rotations were measured in chloroform solution. The microanalyses were carried out by Geller Laboratories, Hackensack, N. J. and Spang Microanalytical Laboratory, Plymouth, Mich.

the condenser was replaced and refluxing was continued for an additional 2.5 hours. After cooling and dilution with water, the crystalline precipitate was collected (0.9 g., m.p. 80–85°) and recrystallized three times from methanol; m.p. 90–93°, $[\alpha]_D^{24}$ −124° no infrared carbonyl band, λ_{max}^{EtOH} 223 mμ, log ε 3.77.

Anal. Calc'd for $C_{19}H_{26}O$: C, 84.39; H, 9.69.

Found: C, 84.69; H, 9.73.

Condensation[5] of furfural with cafestol derivatives. A solution of 190 mg. of the diketone (XI) (1, 2) in 10 cc. of 95% ethanol was treated successively with 0.4 cc. of 15% aqueous sodium hydroxide solution, 0.11 cc. of redistilled furfural, and 1 cc. of water. After 2 hours at room temperature, water was added and the precipitated solid was filtered and washed well with 50% ethanol, dilute acetic acid and finally water; yield, 210 mg., m.p. 160–165°. Several recrystallizations from methanol raised the m.p. to 166–172°, $[\alpha]_D^{24}$ +67°, $\lambda_{max}^{CHCl_3}$ 5.78, 5.89 and strong band at 6.16 μ, λ_{max}^{EtOH} 332 mμ, log ε 4.54.

Anal. Calc'd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46.

Found: C, 77.50; H, 7.60.

Epoxynorcafestadienone was recovered in 92% yield when treated with furfural under the above conditions.

Hypoiodide oxidation of epoxynorcafestadienone. To 5.0 g. of epoxynorcafestadienone dissolved in 225 cc. of pure methanol was added with stirring at room temperature over a period of 1.5 hours simultaneously from two separatory-funnels a solution of 17.5 g. of iodine in 225 cc. of methanol and one of 15 g. of potassium hydroxide in 15 cc. of water and 225 cc. of methanol. After completion of addition, stirring was continued for 1.5 hours and the mixture then was poured into 2 l. of water containing hydrochloric acid. The acid was extracted with chloroform, washed with thiosulfate, and then removed with dilute alkali. The alkaline extracts were acidified with acetic acid and the precipitated acid was recrystallized from dilute acetone; yield, 3.5 g., m.p. 240–245° (capillary). Further recrystallization from acetone afforded the analytical sample, m.p. 225–228° (248–250° capillary), $[\alpha]_D^{25}$ +40° (pyridine), λ_{max}^{EtOH} 223 mμ, log ε 3.87.

Anal. Calc'd for $C_{19}H_{24}O_5$: C, 68.85; H, 7.28.

Found: C, 68.58; H, 7.51.

A sample of the acid was methylated with diazomethane and the *dimethyl ester* was recrystallized from dilute methanol; m.p. 122–125°, $[\alpha]_D^{24}$ +77°. The analytical sample was sublimed at 145° and 0.05 mm.

Anal. Calc'd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83.

Found: C, 70.18; H, 7.93.

Dehydrogenation studies. An intimate mixture of 7.0 g. of the above diacid and 7.0 g. of 5% palladized-charcoal catalyst (American Platinum Works, Newark, N. J.) was heated in an atmosphere of nitrogen for 3.5 hours at 360–400°. The reaction mixture was extracted ten times with boiling hexane and the extracts were washed first with dilute sodium bicarbonate and then with 5% sodium hydroxide solution. The alkaline solution was washed with ether (discarded) and then acidified. The crude phenol (60 mg., m.p. 112–120°) was filtered and alternatively recrystallized (hexane) and sublimed (120°/.01 mm.) four times, whereupon 8.0 mg. of colorless crystals were obtained, m.p. 163–165°, ultraviolet absorption spectrum (Fig. 1). The recorded (9) melting point for 2-phenanthrol is 168°, but a sample prepared according to Fieser's procedure (9) had m.p. 173–173.5° (Kofler); the mixture melted at 163–165° and the x-ray diffraction patterns[11] were very similar.

Anal. Calc'd for $C_{14}H_{10}O$: C, 86.57; H, 5.19.

Found: C, 86.48; H, 5.65.

In another dehydrogenation, 5.0 g. each of the diacid and 5% palladized charcoal was heated for one hour each at 200°, and finally at 300–320°. The mixture was extracted in a Soxhlet apparatus with hexane and the crude phenol (200 mg.) was sublimed at 120° and

[11] Carried out through the courtesy of Dr. J. A. Moore, Parke, Davis and Co., Detroit, Mich.

0.01 mm., yielding 170 mg., m.p. 120–140°, raised to 137–145° after two recrystallizations from hexane. The analytical sample was sublimed three times and recrystallized from dilute ethanol from which it separated in 1-cm. long needles; yield, 50 mg., m.p. 150.5–152°, ultraviolet absorption spectrum in Fig. 1.

Anal. Calc'd for $C_{16}H_{14}O$: C, 86.45; H, 6.35.
Calc'd for $C_{17}H_{16}O$: C, 86.40; H, 6.83.
Found: C, 86.51, 86.15; H, 6.33, 6.56.

A sample of the phenol was treated with 3,5-dinitrobenzoyl chloride in pyridine solution and the yellowish *3,5-dinitrobenzoate* was recrystallized from ethyl methyl ketone; m.p. 247–248°.

Anal. Calc'd for $C_{23}H_{16}N_2O_6$: C, 66.34; H, 3.87; N, 6.73.
Calc'd for $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51.
Found: C, 66.63, 66.59; H, 4.25, 4.18; N, 6.62.

Ultraviolet absorption data.[12] All spectra were measured in absolute ethanol solution with an automatically recording Warren Spectracord attached to a Beckman DU spectrophotometer. The results are given graphically in Fig. 1, but the actual values for the four most important compounds are listed below, the log ϵ values being given in parentheses.

2-Phenanthrol: maxima, 230 (4.20), 255 (4.82), 292 (4.15), 323 (2.76), 339 (3.00), and 355 mμ (3.00); minima, 227 (4.18), 233 (4.15), 286 (4.02), 316 (2.60), 328 (2.66), and 349 mμ (2.66).

3-Phenanthrol: maxima, 248 (4.85), 277 (4.39), 305 (4.28), 340 (3.43), and 355 mμ (3.28); minima, 235 (4.60), 273 (4.26), 292 (4.10), 330 (3.04), and 350 mμ (3.04).

Phenol (m.p. 163–165°) from dehydrogenation: maxima, 230 (4.20), 255 (4.86), 292 (4.16), 324 (2.75), 339 (3.04), and 355 mμ (3.04); minima, 227 (4.16), 233 (4.11), 286 (4.05), 315 (2.58), 328 (2.68), and 349 mμ (2.68).

Phenol (m.p. 150.5–152°) from dehydrogenation: maxima, 231 (4.35), 260 (4.83), 292 (4.12), 328 (2.88), 345 (3.10), and 362 mμ (3.05); minima, 229 (4.30), 237 (4.10), 290 (4.10), 319 (2.62), 333 (2.80), and 352 mμ (2.88).

Isolation of cafestol from African coffee oil. The extraction of 287 g. of African coffee oil (General Foods Corporation, Hoboken, N. J.) was carried out exactly as described for Santos coffee oil (1) and yielded 8.15 g. of crystalline solid, m.p. 140–150° with softening starting at 80°. One recrystallization from ether gave 4.6 g. of cafestol, m.p. 145–156°, $[\alpha]_D^{24}$ −101°, λ_{max}^{EtOH} 223 mμ, log ϵ 3.86; no other maximum was observed but there was an inflection at 285–290 mμ, log ϵ 2.55. Acetylation in the standard manner and two recrystallizations from methanol led to cafestol acetate with the following constants indicating the virtual absence of kahweol: m.p. 162–166°, λ_{max}^{EtOH} 224 mμ, log ϵ 3.84, inflection near 290 mμ, log ϵ 2.00.

Anal. Calc'd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44.
Found: C, 73.39; H, 8.34.

C-Methyl determinations. The Kuhn-Roth C-methyl values obtained in different analytical laboratories are given below and are sufficiently low so that some doubt might be expressed as to whether a C-methyl group is indeed present in cafestol (*e.g.* XIV). C-methyl calculated: cafestol, 4.7%; epoxynorcafestadienone, 5.3%; dibasic acid (*e.g.* XX), 4.5%.

Laboratory A: Found: dibasic acid, 0.49%.

Laboratory B: Found: dibasic acid, 0.79%; epoxynorcafestadienone, 0.66%.

Laboratory C: Found: epoxynorcafestadienone, 0.0%; santonin (run for comparison under identical conditions), 10.45%.

Laboratory D: Found: cafestol, 1.1%; epoxynorcafestadienone, 1.1%; dibasic acid, 0.9%; dehydroepiandrosterone (run for comparison under identical conditions (2.7%)).
When the oxidation time was increased from 2 to 4 hours, cafestol gave 1.5% while the steroid standard remained unchanged. A blank run using lactose yielded no volatile acid.

---

[12] We are indebted to Dr. L. F. Fieser (Harvard University) and Dr. Erich Mosettig (National Institutes of Health) for supplying some of the comparison samples.

Acknowledgment: We are greatly indebted to General Foods Corporation, Hoboken, New Jersey for assistance in the form of fellowships and to Dr. H. M. Barnes of that company for generous supplies of coffee oil.

SUMMARY

Dehydrogenation of a cafestol derivative has led to substituted 2-phenanthrols, thus constituting the first, direct chemical evidence for the presence of a pentacyclic skeleton in this constituent of coffee oil. A partial structure for cafestol is advanced, only the attachment of the cyclopentane ring being left open for further consideration.

DETROIT, MICHIGAN

REFERENCES

(1) DJERASSI, WILFRED, VISCO, AND LEMIN, *J. Org. Chem.*, **18**, 1449 (1953).
(2) WETTSTEIN, HUNZIKER, AND MIESCHER, *Helv. Chim. Acta*, **26**, 1197 (1943).
(3) HAWROTH, JUBB, AND MCKENNA, *Chemistry & Industry*, 104 (1954).
(4) BLADON, HENBEST, AND WOOD, *J. Chem. Soc.*, 2737 (1952).
(5) HAUPTMANN AND FRANCA, *Z. physiol. Chem.*, **259**, 245 (1939).
(6) KING AND KING, *J. Chem. Soc.*, 4158 (1953).
(7) WETTSTEIN, FRITZSCHE, HUNZIKER, AND MIESCHER, *Helv. Chim. Acta*, **24**, 332E (1941).
(8) WETTSTEIN AND MIESCHER, *Helv. Chim. Acta*, **26**, 631 (1943).
(9) FIESER, *J. Am. Chem. Soc.*, **51**, 2460 (1929) and references cited therein.