[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF OHIO STATE UNIVERSITY, COLUMBUS, O., AND STANFORD UNIVERSITY, STANFORD, CALIF.]

Terpenoids. XLV.[1] Further Studies on the Structure and Absolute Configuration of Cafestol[2]

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Peracid oxidation of epoxynorcafestanone (II) afforded the lactone VII, which was opened to the hydroxy acid VIIIa, methylated and then oxidized to yield the keto methyl ester IX. This sequence establishes unambiguously the location of the glycol grouping in the five-membered ring of cafestol. The optical rotatory dispersion curve of IX affords additional evidence on the stereochemistry of the B/C/D ring junctures and thus confirms the earlier proposed[3] absolute configuration (I) of this diterpenoid.

Recently,[3] we proposed structure I as a complete expression for the constitution and absolute configuration of the diterpene cafestol. The perhydrophenanthrene skeleton encompassed by rings A, B and C, the location of the angular methyl group at C-10, and finally the connection of the furan ring to positions 3 and 4 were settled by a variety of unambiguous degradations. Furthermore, the absolute configuration of the A/B ring juncture—antipodal to that of the steroids—followed directly from optical rotatory dispersion studies.[3-5]

The attachment of the five-membered ring of cafestol to C-8 and C-13 as well as the location of the glycol grouping at C-16 (rather than C-15) rested on more circumstantial evidence,[3] notably the remarkable coincidence of the rotatory dispersion curves[4] of epoxynorcafestanone (II)[6] and the norketone IV[7] derived from phyllocladene (III). Brandt's structure proposal[7,8] for phyllocladene (III) has recently been confirmed by interrelation with abietic acid[9] and with manool[10] thus affording a reference compound for optical rotatory dispersion comparisons. However, before such comparisons between analogous ketonic derivatives of cafestol and phyllocladene are justified, it is necessary that the condition[5] of identical absolute configuration and conformation around the immediate environment of the carbonyl chromophore be met.

Insofar as phyllocladene (III) is concerned, the absolute configuration[10,11] implied in stereoformula III (using the usual steroid notation) is derived from two arguments: (a) The absolute configuration of carbon atoms 5 and 10 follows rigorously from the reported interconversion[9,10] with abietic acid and manool, while that of C-9 is probably but not necessarily as indicated in III. (b) Phyllocladene has been converted[7,8] into a keto acid, which now can be represented by V or VI, depending upon the absolute configuration of C-8. As pointed out earlier,[3] the octant rule[12] predicts a positive Cotton effect for V and a negative one for VI, as well as for the 9β-isomers of V and VI. Since the keto acid from phyllocladene exhibits[3] a positive rotatory dispersion Cotton effect curve, the absolute configuration of phyllocladene at C-8, C-9 and *ipso facto* at C-13 is settled.

Turning now to cafestol (I), since its A/B ring juncture is antipodal to that of phyllocladene (III), the coincidence of the rotatory dispersion curves of their derived nor-ketones II and IV implies[13] that the two diterpenes possess identical absolute configurations at carbon atoms 8, 9 and 13 and it was for this reason that the complete stereoformula I was proposed.[3] This assignment leads to a 9,10-*syn* backbone in cafestol, which in turn requires that ring B exist in a boat form and the behavior of certain derivatives of cafestol was found[3] to be consistent with such a stereochemical feature. Nevertheless, it was deemed highly desirable to secure independent evidence for the stereochemistry of the B/C/D ring fusion of cafestol, and experiments bearing on this point are reported herewith.

Oxidation of epoxynorcafestanone (II)[6] with peroxytrifluoroacetic acid[14] furnished a crystalline δ-lactone, which had to possess structure VII or X, depending upon whether the original glycol grouping of cafestol is located at C-16 or C-15. Alkaline opening of the lactone followed by cautious acidification led to a crystalline hydroxy acid VIIIa, which was transformed into its oily methyl ester VIIIb. The latter could not be purified by chromatography, since even neutral alumina caused relactonization[15] and the ester was, therefore, directly oxidized with chromium trioxide in pyridine[16] to yield a crystalline keto ester. *The forma-*

(1) Paper XLIV, D. Herbst and C. Djerassi, THIS JOURNAL, **82**, 4337 (1960).

(2) Supported in part by grant No. RG-6840 from the National Institutes of Health, U. S. Public Health Service.

(3) C. Djerassi, M. Cais and L. A. Mitscher, THIS JOURNAL, **81**, 2386 (1959); for preliminary communication see *ibid.*, **80**, 247 (1958).

(4) C. Djerassi, R. Riniker and B. Riniker, *ibid.*, **78**, 6362 (1956).

(5) C. Djerassi, "Optical Rotatory Dispersion. Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, Chapter 10.

(6) A. Wettstein, F. Hunziker and K. Miescher, *Helv. Chim. Acta*, **26**, 1197 (1943); see also R. D. Haworth, A. H. Jubb and J. McKenna, *J. Chem. Soc.*, 1983 (1955).

(7) C. W. Brandt, *New Zealand J. Sci. Tech.*, **34B**, 46 (1952); see also W. Bottomley, A. R. H. Cole and D. E. White, *J. Chem. Soc.*, 2624 (1955).

(8) See also L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *Tetrahedron Letters*, *No. 8*, 8 (1959).

(9) L. H. Briggs, B. F. Cain and R. C. Cambie, *ibid.*, *No. 8*, 17 (1959).

(10) P. K. Grant and R. Hodges, *ibid.*, *No. 10*, 21 (1959).

(11) L. H. Briggs, B. F. Cain, B. R. Davis and J. K. Wilmshurst, *ibid.*, *No. 8*, 13 (1959).

(12) W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne and C. Djerassi, to be published; for details see chapter 13 in ref. 5.

(13) See footnote 61 in ref. 3.

(14) W. D. Emmons and G. B. Lucas, THIS JOURNAL, **77**, 2287 (1955).

(15) Relactonization of a γ-hydroxy ester on alumina was observed recently by F. Sondheimer, N. Stjernström and D. Rosenthal, *J. Org. Chem.*, **24**, 1280 (1959).

(16) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

tion of this keto ester IX represents the first direct chemical proof that the glycol grouping of cafestol is attached at C-16 (see I). If it were located at C-15, then the derived lactone X could not have been convertible to a keto ester.

The keto ester IX also offers a means of examining the stereochemistry of carbon atoms 8 and 9. It has been demonstrated numerous times[5] that the nature of an angular substituent in an optically active decalone has no important effect on the over-all shape of the rotary dispersion curve, the controlling factor being its stereochemistry. Indeed this equating of an angular methyl group with an angular acetic acid moiety offered the key to the elucidation of the absolute configuration of gibberellic acid[17] and of steviol[18] by means of the rotatory dispersion curves of appropriate ketonic degradation products. As shown in the Experimental section, the keto ester IX exhibited a positive Cotton effect in methanol solution.

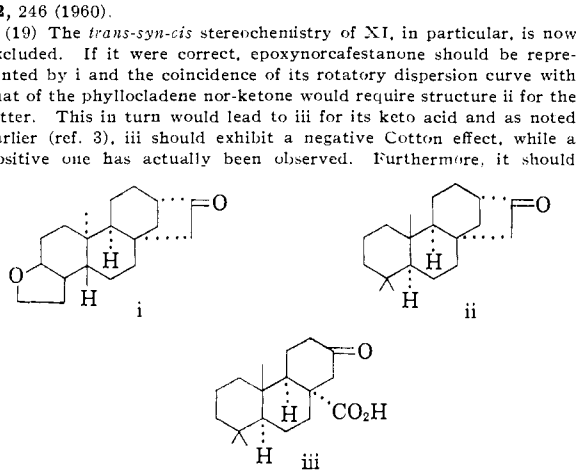
Since the stereochemistry at positions 5 and 10 of cafestol (I) has aleady been established,[3] there remain only four stereochemical alternatives (involving C-8 and C-9) for the keto ester (IX, XI, XII, XIII). According to the octant rule,[12] one would predict positive Cotton effects for IX, XI and XII, while a negative one is expected for XIII. In view of the observed positive Cotton effect, XIII can immediately be eliminated from further consideration and cafestol cannot possess a *trans-anti-trans* A/B/C skeleton.

Admittedly, the rotatory dispersion curve of the keto ester *per se* does not distinguish among the three remaining possibilities IX, XI and XII. However, when taken in conjunction with the coincidence[4] of the rotatory dispersion curves of epoxynorcafestanone (II), and the nor-ketone IV from phyllocladene, the evidence now appears to be overwhelmingly in favor of the earlier proposed[3] stereoformula I for cafestol.[19]

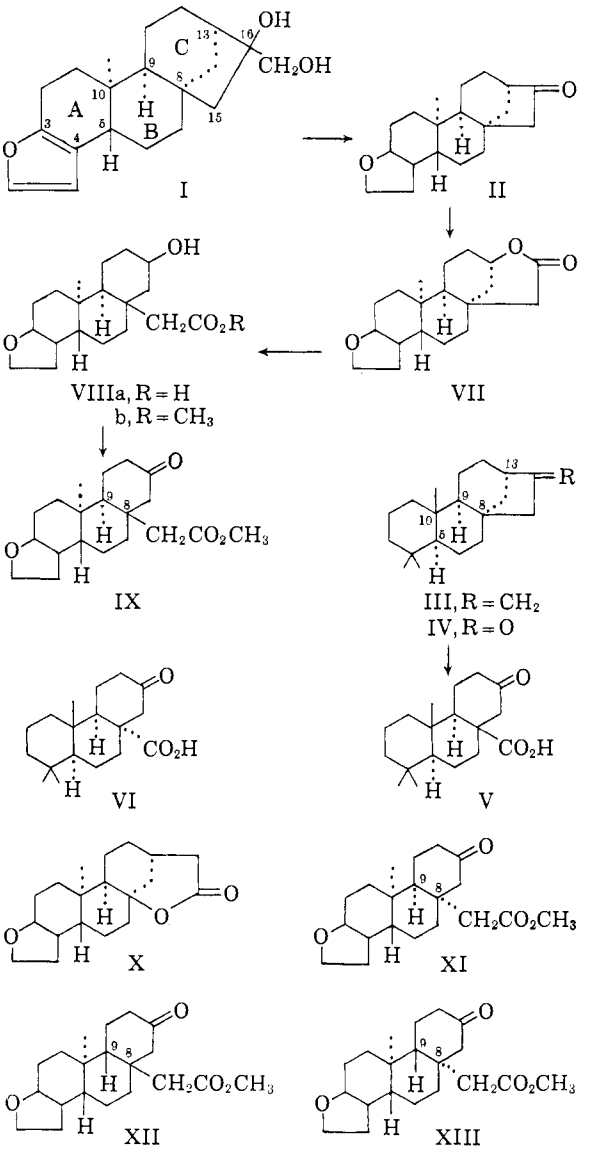
(17) G. Stork and H. Newman, THIS JOURNAL **81**, 3168, 5518 (1959); B. E. Cross, J. E. Grove, P. McCloskey, T. P. C. Mulholland and W. Klyne, *Chemistry & Industry*, 1345 (1959).

(18) F. Dolder, H. Lichti, E. Mosettig and P. Quitt, THIS JOURNAL, **82**, 246 (1960).

(19) The *trans-syn-cis* stereochemistry of XI, in particular, is now excluded. If it were correct, epoxynorcafestanone should be represented by i and the coincidence of its rotatory dispersion curve with that of the phyllocladene nor-ketone would require structure ii for the latter. This in turn would lead to iii for its keto acid and as noted earlier (ref. 3), iii should exhibit a negative Cotton effect, while a positive one has actually been observed. Furthermore, it should



be noted that while the keto ester XI can exist in an all-chair conformation, the corresponding lactone or the cyclic ketone i require a boat conformation of rings B or C. While lactonization of a γ-hydroxy ester with concomitant chair-to-boat inversion has been observed (C. Djerassi and J. S. Mills, THIS JOURNAL, **80**, 1236 (1958)), the ease of relactonization of the δ-hydroxy ester VIIIb would tend to favor a formulation based on IX, XII or XIII (where no conformational change is required) rather than XI.



Experimental[20]

Peracid Oxidation of Epoxynorcafestanone (II).—To a mixture of 1.28 g. of epoxynorcafestanone (II)[6] (m.p. 129–131°, λ_{max}^{KBr} 5.69 μ, λ_{max}^{EtOH} 292 mμ, ε 26), 6 cc. of methylene chloride and 2.9 g. of disodium hydrogen phosphate was added slowly with swirling over a period of **15** min. a solution of 0.20 cc. of 90% hydrogen peroxide and 1.15 cc. of trifluoroacetic anhydride in 6 cc. of methylene chloride. After heating under reflux for 1 hr., the mixture was filtered, washed with 10 cc. of 10% aqueous sodium carbonate solution, dried and evaporated. The resulting colorless oil was chromatographed on 120 g. of Merck acid-washed alumina and after eluting 0.28 g. of recovered epoxynorcafestanone with benzene–ether (1:1), the **lactone VII** (0.63 g., m.p. 175–181° after recrystallization from chloroform–ligroin) was obtained in the ether fraction.

Recrystallization or repeated chromatography did not raise the m.p. above 181° and while the lactone's infrared spectrum was identical with that of the analytical specimen, purification was best accomplished as follows. The lactone was heated under reflux for 12 hr. with 8% methanolic potas-

(20) Melting points are uncorrected (Fisher–Johns block). The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany.

sium hydroxide solution, cooled, diluted with water and extracted with ether (discarded). The aqueous layer was acidified, extracted with ether and the residue from the washed and dried ether extract was dissolved in methanol containing a few drops of concd. sulfuric acid. After heating for 24 hr., water was added and the **lactone VII** was extracted with ether and recrystallized several times from chloroform–ligroin; m.p. 184–186°, $[\alpha]^{25}D$ −31° (*c* 0.47 in $CHCl_3$), λ_{max}^{KBr} 5.76 μ (no hydroxyl band).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.97. Found: C, 74.78; H, 9.01; O, 15.80.

Conversion of Lactone VII to Keto Ester IX.—The above lactone VII (0.6 g.) was heated under reflux for 12 hr. with 15 cc. of methanol, 10 cc. of water and 2.0 g. of potassium hydroxide, cooled, diluted with water and extracted with ether. The aqueous layer was cooled in ice[21] and over a period of 1 hr. there was added slowly with stirring 36 cc. of 1 *N* sulfuric acid. Extraction with chloroform, drying and evaporation afforded 0.51 g. of the **hydroxy acid VIIIa**, m.p. 150–153° after one recrystallization. Three recrystallizations from chloroform–ligroin led to 0.17 g. of the analytical specimen, m.p. 157–161°,[22] λ_{max}^{KBr} 2.87 and 5.76 μ (as well as typical broad "acid" absorption in 3.6 μ region).

Anal. Calcd. for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38; O, 19.85. Found: C, 70.37; H, 9.27; O, 20.04.

Methylation of 89 mg. of the hydroxy acid (m.p. 150–153°) with excess ethereal diazomethane solution afforded the **hydroxy ester VIIIb** as a colorless resin. Chromatography on 10 g. of Woelm neutral alumina (activity III) and elution with benzene and benzene–ether (9:1) led after recrystallization from chloroform–ligroin to 62 mg. of the lactone VII, m.p. 176–179°.

Consequently in a second experiment, the methyl ester from 140 mg. of hydroxy acid VIIIa was not chromatographed, but the crude oily ester ($\lambda_{max}^{capill.}$ 2.80 and 5.77 μ) obtained on washing the ether solution with sodium bicarbonate, was treated directly at 0° with 100 mg. of chromium trioxide in 10 cc. of pyridine. The mixture was allowed to warm to room temperature and was then stirred for 9 hr. before dilution with water. After cooling in ice and acidifying slowly with 25% sulfuric acid, the product was extracted with ether, washed with sodium bicarbonate and water, dried and evaporated. The residue was chromatographed on 12 g. of Merck acid-washed alumina and the pooled benzene–ether (1:1) eluates were evaporated (80 mg., m.p. 55–64° after one recrystallization) and recrystallized eight times from chloroform—hexane to afford 37 mg. of the **keto ester IX**, m.p. 78–80°, λ_{max}^{KBr} 5.73 and 5.79 μ; R.D. in methanol (*c* 0.095): $[\alpha]_{700}$ +13°, $[\alpha]_{589}$ +29°, $[\alpha]_{312.5}$ +643°, $[\alpha]_{270}$ −357°, $[\alpha]_{255}$ −155°.

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04; O, 19.14. Found: C, 71.92; H, 9.15; O, 19.35.

(21) When the acidification was conducted rapidly at room temperature, a mixture of lactone VII and hydroxy acid VIIIa was obtained.

(22) The melting point of the hydroxy acid varied with the rate of heating. When heated very slowly, melting commenced at 154° with gas evolution, the melt resolidifying partially and then showing m.p. 178–187°, presumably due to lactonization. Rapid heating of a specimen placed on a preheated block of 140° showed m.p. 160–164°.

[CONTRIBUTED FROM THE NATIONAL RESEARCH CENTER, CAIRO, EGYPT]

The 4-Pyrones. Part I. Reactions of Some 4-Pyrones and 4-Thiopyrones Involving the Ring Oxygen

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4-Pyrones and 4-thiopyrones react with N-alkylamines to give N-alkylpyridones and N-alkylthiopyridones, respectively. The N-alkylpyridones do not react with carbonyl or Grignard reagents. When brominated they give the dibromo derivatives, the bromine of which could not be removed by alkali and did not react as aromatic bromine when treated with magnesium. N-Alkyl-2,6-diphenyl-4-pyridone is not hydrolyzed with hydrochloric acid but can be converted to the corresponding thione by the action of phosphorus pentasulfide. The N-alkyl-4-thiopyridones, when oxidized with perhydrol, give the corresponding anhydrosulfonic acids.

The 4-pyrones react with hydrazines to form pyrazoles,[1,2] with hydroxylamine to give hydroxypyridones[3] and with ammonia to give pyridones.[4]

We have found that methylamine or ethylamine react with the pyrones (Ia, IIa and IIIa) to give the N-methyl- or N-ethylpyridones (VI, VII and VIIa or b).

The thiopyrones (Ib, IIb, IIIb and IVb) were found to react with the same reagents to give the corresponding thiopyridones (VI, VII, VIII and IXc or d).

The formation of the N-hydroxy- or N-alkylpyridones as well as the N-alkylthiopyridones may be represented by the scheme A–E.

The non-reactivity of 2,6-di-*p*-methoxyphenyl-4-pyrone (IVa) may be attributed to the partial compensation of the positive charge in structure A by the +T effect of the two methoxyl groups in the *p*-positions, 2-*p*-methoxyphenyl-6-phenyl-4-pyrone (IIIa) being less readily convertible to the pyridone than the 2,6-diphenyl-4-pyrone. Conversely, the

a, A = X = O
b, A = O, X = S
c. A = O, X = NOH
a, X = O, R'' = CH_3
b, X = O, R'' = C_2H_5
c, X = S, R'' = CH_3
d, X = S, R'' = C_2H_5
e, X = O, R'' = OH
I, R = R' = CH_3
II, R = R' = C_6H_5
III, R = C_6H_5; R' = $C_6H_4OCH_3(p)$
IV, R = R' = $C_6H_4OCH_3(p)$
V, R = C_6H_5; R' = $C_6H_4Br(p)$
VI, R = R' = CH_3
VII, R = R' = C_6H_5
VIII, R = C_6H_5; R' = $C_6H_4OCH_3(p)$
IX, R = R' = $C_6H_4OCH_3(p)$
X, R = C_6H_5; R' = $C_6H_4Br(p)$

reactivity of the 2,6-di-*p*-methoxyphenyl-4-thiopyrone may be attributed to the stronger −T effect of the C=S group as compared to that of the C=O

(1) R. G. Jones and M. J. Mann, THIS JOURNAL, **75**, 4048 (1953).
(2) C. Ainsworth and R. G. Jones, *ibid.*, **76**, 3172 (1954).
(3) G. Soliman and I. E-S. El-Kholy, *J. Chem. Soc.*, 1755 (1954).
(4) L. Neelakantan, *J. Org. Chem.*, **23**, 741 (1958).