electrometric titrations by Dr. M. J. Allen, formerly of the CIBA Chemical Research Division; paper chromatograms by Mr. B. Korzun and co-workers; biological tests on the esters of methyl *neo*-reserpate by Dr. A. J. Plummer and Dr. W. Barrett of the CIBA Macrobiologic Division; technical assistance by Mr. M. P. Linfield.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

# The Absolute Configuration of the Glycol Grouping in the Diterpene Cafestol

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Epoxynorcafestanone (III) was converted stereospecifically, *via* the olefin VI, to tetrahydrocafestol (II). This reaction sequence allows the (R)-configuration to be assigned to C-16 of the diterpene cafestol.

Cafestol, the pentacyclic diterpene constituent of coffee oil, recently[1] has been assigned structure and absolute configuration I, in which the configuration of all asymmetric centers save C-16 has been assigned. The configuration at the A/B ring fusion (antipodal to the steroids) was unambiguously determined by means of optical rotatory dispersion studies.[1,2] The establishment of configuration at the B/C/D ring junctures rested primarily on the coincidence of the rotatory dispersion curves[3] of the norketone III[4,5] derived from cafestol (I) and the norketone IV[6,7] derived from phyllocladene (V), whose absolute configuration has been assigned as indicated in V.[8-10] Subsequent degradative experiments coupled with rotatory dispersion measurements afforded additional evidence for the configuration at the B/C/D ring junctures as depicted in I.[11]

The present work demonstrates that the remaining asymmetric center at C-16 has the (R)-configuration[12] as indicated in VII.[13]

The norketone (III, epoxynorcafestanone) obtained by lead tetraacetate cleavage of tetrahydrocafestol (II)[14] was converted to the olefin (VI) by treatment with Wittig's reagent. The structure of VI, which was apparent from its method of formation as well as by its subsequent transformations, was confirmed by microanalysis and by its infrared spectrum. Hydroxylation of VI with osmium tetroxide led to a single glycol (VII, purified *via* its acetate, VIIa) whose relative configuration followed from consideration of the steric course of the hydroxylation step. Molecular models of the olefin VI (*cf.* VIII) indicate that attack at C-16 from the $\beta$-face of the molecule is severely hindered by the axial hydrogen atom attached to C-11. The large steric demands of osmium tetroxide in the formation of the intermediate cyclic osmate ester therefore require attack from the side of the methylene bridge; thus, the resulting glycol must have the (relative) configuration shown in VII (C-16 hydroxyl *cis* to the methylene bridge). This argument is supported by the high degree of stereospecificity actually observed. Infrared examination of the crude synthetic glycol and its acetate, as well as materials recovered from the mother liquors, failed to reveal the presence of an epimeric compound. As the synthetic glycol (VII) and its acetate (VIIa) proved to be identical, respectively, with tetrahydrocafestol (II) and tetrahydrocafestyl acetate (IIa), the natural product has the configuration depicted in VII. That this also represents the *absolute* configuration follows from the previously assigned absolute configuration of the methylene bridge.

This result accords nicely with the scheme pro-

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(9) L. H. Briggs, B. F. Cain, and R. C. Cambie, *Tetrahedron Letters*, **8**, 17 (1959).

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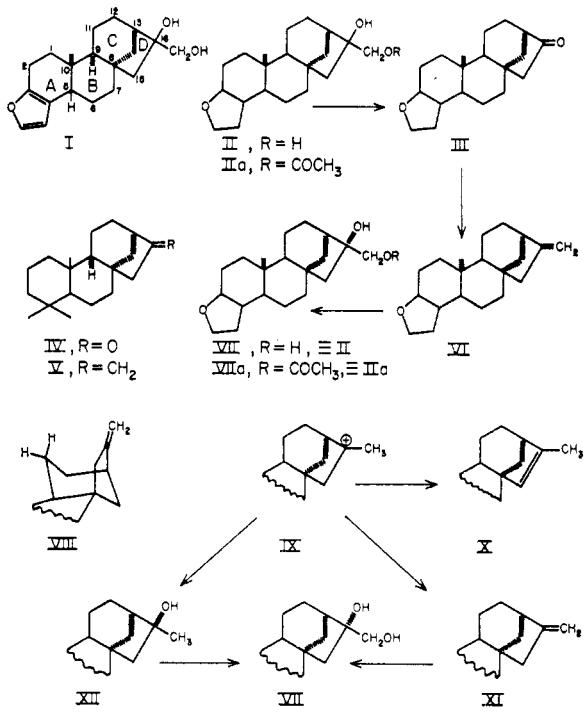
(13) Preliminary communication of these results has been made. R. A. Finnegan, Abstracts of Papers, 138th Meeting of the American Chemical Society, New York, N. Y., September 13, 1960, p. 28P.

(14) No configuration is implied for the points of attachment of the tetrahydrofuran moiety to ring A.



posed[15,16] for the biogenesis of the phyllocladene class of diterpenes. In this scheme, the carbonium ion IX occurs as an intermediate leading to the olefin X (*e.g.*, isophyllocladene) or XI (*e.g.*, phyllocladene V or olefin VI) by proton expulsion. Enzymatic hydroxylation of XI from the least hindered side would afford VII with the correct stereochemistry. Alternately, the ion IX may be solvolyzed, again from the least hindered side, forming the alcohol XII, which may then be converted to VII by oxidation of the methyl group. The isolation from coffee oil of the olefins X or XI (or the alcohol XII) corresponding to cafestol would provide interesting evidence for the existence of these pathways.

## EXPERIMENTAL[17]

*Tetrahydrocafestyl acetate* (IIa). Crude cafestyl acetate[18] was purified and hydrogenated by known methods.[5] The product, after chromatography on alumina and recrystallization from chloroform-ligroin, had m.p. 151–153°, (lit.[19] m.p. 153–154°).

*Tetrahydrocafestol* (II). After saponification with methanolic potassium carbonate, the acetate IIa afforded the glycol II; m.p. 157–159° after recrystallization from chloroform-ligroin, (lit.[5] m.p. 156–157°).

*Epoxynorcafestanone* (III). Tetrahydrocafestol was treated with lead tetraacetate in benzene solution and the product norketone purified by chromatography and recrystallization, m.p. 129–131°; $\nu_{max}^{KBr}$ 1757 cm.$^{-1}$ (no hydroxyl). (Lit.[5] m.p. 129–130°.)

*Reaction of epoxynorcafestanone with Wittig's reagent; preparation of the olefin* VI. A solution of epoxynorcafestanone (0.25 g., 0.88 mmole) in ether (10 ml.) was added to an ether solution (50 ml.) of Wittig's reagent that had been prepared by treatment of methyltriphenylphosphonium iodide (1.23 g., 3 mmoles) with 1*N* butyllithium solution (3 ml.). After the mixture had refluxed for 1 hr., acetone was added until the color was discharged. The reaction mixture was filtered four times (with petroleum ether, b.p. 60–68° added) to remove the precipitate of triphenylphosphine oxide. The filtrate was evaporated and the residual oil was chromatographed on 20 g. Merck acid washed alumina. From the petroleum ether eluate was obtained a small amount of crystalline material, m.p. 75–79°, shown to be triphenylphosphine by mixed melting point and infrared comparison with an authentic sample. The olefin VI which was eluted in petroleum ether: benzene mixtures (19:1 and 9:1), crystallized on trituration with ether, m.p. 60–64°, 0.11 g. Two additional recrystallizations from either a methylene chloride-petroleum ether (b.p. 30–60°) mixture or from a chloroform-hexane mixture gave the product, m.p. 65–67°, $\nu_{max}^{KBr}$ 1664(m) and 864 (s) cm.$^{-1}$ A sample dried for analysis had m.p. 66–67°.

*Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.50; H, 10.54.

Continued elution of the column with benzene-ether mixtures resulted in the recovery of 60 mg. of the starting norketone. In other experiments the crude product mixture was resubmitted to the Wittig reaction conditions (two times) until the product showed no carbonyl absorption in the infrared. This treatment, followed by chromatographic purification, afforded 0.17 g. crystalline olefin from 0.4 g. starting norketone.

*Reaction of the olefin with osmium tetroxide, formation of the glycol* VII. The olefin (104 mg., 0.39 mmole) was dissolved in pyridine (5 ml.) with with osmium tetroxide (0.5 g., 1.97 mmoles). After being stirred at room temperature for 5 hr., the reaction mixture was worked up according to the procedure of Baran.[20] Thus, a solution containing 1 g. of sodium bisulfite in 15 ml. of water with 13 ml. of pyridine was added to the osmylation mixture and stirring was continued for 50 min. before the dark colored solution was extracted with chloroform. The chloroform extracts were dried and evaporated to give the glycol, m.p. 145–160° (116 mg.).

*Acetylation of the synthetic glycol. Preparation of* VIIa. The crude glycol (above) was dissolved in pyridine (10 ml.) with acetic anhydride (5 ml.) and allowed to stand for 16 hr. at room temperature. After the usual work up, there was obtained a solid, which was chromatographed on 15 g. Merck acid washed alumina. The main band eluted in ether afforded 124 mg. crystalline acetate, m.p. 135–147°. After seven recrystallizations from chloroform-hexane mixtures, there was obtained 10 mg. material, m.p. 150–153° alone or admixed with authentic tetrahydrocafestyl acetate (IIa). The infrared spectra (potassium bromide) of the two samples were indistinguishable. An additional amount (52 mg., m.p. 143–149°) was obtained from the mother liquors whose infrared spectrum was also identical with that of the naturally derived acetate.

*Saponification of the synthetic acetate, regeneration of* VII. The acetate VIIa (45 mg.) was dissolved in methanol (3 ml.) with water (3 ml.) and potassium carbonate (0.5 g.). The solution was refluxed for 8.5 hr. before it was poured into 50 ml. water and extracted with ether. The ether extracts were dried and evaporated, giving a white solid, m.p.

(15) L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmhurst, *Tetrahedron Letters*, **8**, 13 (1959).

(16) E. Wenkert, *Chem. & Ind.*, 282 (1955).

(17) The melting points are uncorrected (Fischer-Johns block). The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. The infrared spectra were obtained on a Baird Model B instrument.

(18) The author wishes to express his gratitude to Professor C. Djerassi for a supply of this material.

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149–155°, whose infrared spectrum (potassium bromide) was identical with that of tetrahydrocafestol. After one recrystallization from chloroform-hexane, there was obtained 26 mg. glycol (VII), m.p. 156–158°, undepressed upon admixture with authentic tetrahydrocafestol (II) and having an identical infrared spectrum (potassium bromide).

Infrared examination of the first crude samples of the synthetic glycol and its acetate, as well as of the materials recovered from various mother liquors, failed to reveal the presence of an epimeric compound.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY UNIVERSITY OF ILLINOIS]

# Synthesis of *dl*-Isoretronecanol

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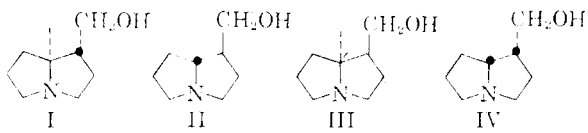
A stereospecific synthesis of *dl*-isoretronecanol is described.

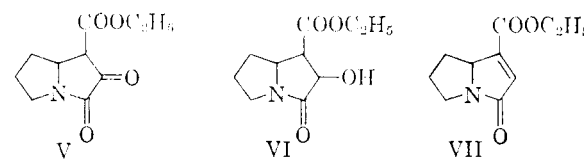
In previous papers[1,2] from this laboratory, the syntheses of 1-hydroxypyrrolizidine and 1-hydroxymethyl-2-hydroxypyrrolizidine were described. The establishment of the absolute configuration of the C-1 atom in heliotridane[3] and retronecanone[4] has permitted the deduction of the absolute configuration of the C-1 atom in a large number of naturally occurring pyrrolizidine alcohols. However, synthesis leading to a stereochemically pure hydroxymethylpyrrolizidine has been accomplished only recently.[5,6]

Altogether four 1-hydroxymethylpyrrolizidines, are known, trachelanthamidine (I), laburnine (II), isoretronecanol (III), and lindelofidine (IV).[7] As the rings in the pyrrolizidine molecule




are inclined at an angle to the plane of the paper along the C—N axis, structures I and II representing trachelanthamidine and laburnine (a pair of enantiomers) are thermodynamically more stable[8] than isoretronecanol and lindelofidine. Except for a very recently reported synthesis[9] of *dl*-isoretronecanol, all previous synthetic methods[5,10] yielded only the racemate which consisted of the thermodynamically more stable trachelanthamidine or laburnine.

We have now accomplished a stereospecific synthesis of *dl*-isoretronecanol. 2,3-Dioxo-1-carbethoxypyrrolizidine (V), prepared by the condensation of diethyl oxalate and ethyl 2-pyrrolidylacetate,[2] was reduced with 5% rhodium on alumina catalyst and hydrogen to 1-carbethoxy-2-hydroxy-3-oxopyrrolizidine (VI). Dehydration using *p*-toluenesulfonyl chloride and pyridine gave 1-carbethoxy-3-oxopyrrolizid-1,2-ene (VII) in good yield. Reduction with rhodium on alumina




catalyst and hydrogen at atmospheric pressure and temperature saturated the olefinic double bond and yielded 1-carbethoxy-3-oxopyrrolizidine. This last product upon treatment with lithium aluminum hydride in tetrahydrofuran gave in good yield 1-hydroxymethylpyrrolizidine, which was *dl*-isoretronecanol. The infrared spectrum of synthetic *dl*-isoretronecanol picrate was identical with that of *l*-isoretronecanol picrate.[11] The spectrum was very similar to but different in detail from that of *dl*-trachelanthamidine. Reaction of *dl*-isoretronecanol with benzoyl chloride yielded *dl*-1-benzoyloxymethylpyrrolizidine as a low melting solid. The infrared spectra of *dl*-1-benzoyloxymethylpyrrolizidine picrate and *l*-benzoylisoretronecanol picrate were superimposable. Treatment of *dl*-isoretronecanol with thionyl chloride yielded *dl*-chloropseudoheliotridane characterized as its picrate.

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