5α,6β,17α-Trichloropregnan-3β-ol-20-one Acetate (VII).[27] —M.p. 194–195°; R.d. (*c* 0.051) in octane: $[\alpha]_{700}$ −59°, $[\alpha]_{589}$ −62°, $[\alpha]_{317.5}$ −579°, $[\alpha]_{275}$ −168°, $[\alpha]_{255}$ −350°.

2α-Fluorocholestan-3-one (IIId),[10] λ_{max}^{MeOH} 280 mμ, log ε 1.25; R.D. (*c* 0.040) in methanol: $[\alpha]_{700}$ +37°, $[\alpha]_{589}$ +65°, $[\alpha]_{309}$ +655°, $[\alpha]_{260}$ −532°; R.D. (*c* 0.042) in octane: $[\alpha]_{700}$ +33°, $[\alpha]_{589}$ +43°, $[\alpha]_{329}$ +904°, $[\alpha]_{280}$ −676°, $[\alpha]_{270}$ −664°.

2α-Iodocholestan-3-one (IIIa),[8] λ_{max}^{MeOH} 256–258 mμ (log ε 2.86),[25] λ_{max}^{hexane} 260–262 mμ (log ε 2.82); R.D. (*c* 0.061) in methanol: $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +59°, $[\alpha]_{315}$ +858°, $[\alpha]_{260}$ −349°.

(27) The preparation of this substance by J. S. Mills and O. Camiliani will be reported in another connection.

APDO. POSTAL 2679, MÉXICO, D. F.,
DETROIT, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Terpenoids. XXXVII.[1] The Structure of the Pentacyclic Diterpene Cafestol. On the Absolute Configuration of Diterpenes and Alkaloids of the Phyllocladene Group[2]

BY CARL DJERASSI, M. CAIS[3] AND L. A. MITSCHER[4]

RECEIVED NOVEMBER 14, 1958

Degradation experiments are reported which establish the structure of cafestol in terms of the expression I. Kahweol, a companion of cafestol, can now be assigned a constitution (XLI) based on the same furanoid phyllocladene system. The absolute configuration of cafestol at C-5 and C-10 has been established by rotatory dispersion measurements and was shown to be *antipodal* to that of the steroids or diterpenes of the abietic acid class. On the basis of rotatory dispersion measurements and other considerations, it is suggested that gibberellic acid, the *Garrya* alkaloids and the alkaloids of the atisine group all are derived from an intermediate which possesses this same sterochemical feature—the C-10 angular substituent between rings A and B being α-oriented, and that this applies probably also to phyllocladene (see ref. 61). Rotatory dispersion also offers some information on the nature of the B/C ring juncture in phyllocladene.

In two recent preliminary communications[5,6] there was outlined evidence which led us to propose structure I for the diterpenoid coffee constituent cafestol. The present paper is concerned with a detailed exposition of the experimental data obtained in support for expression I as well as with a consideration of rotatory dispersion measurements which permit an assignment of absolute configuration to cafestol and most likely also to an entire group of related diterpenes and terpenoid alkaloids.

For the sake of clarity, the structural argument will be presented in terms of structure I, the stereochemistry of C-9 being covered at the end of this paper.

The presence of a furan ring in cafestol was first recognized by Wettstein and Miescher.[7] The existence of a perhydrophenanthrene system and the point of attachment of the furan ring were established in this Laboratory[8] by converting cafestol into epoxynorcafestadienone (II),[9] hypoiodite oxidation to the dibasic acid III and dehydrogenation to an ethylphenanthrol. The latter was shown[5] to be 1-ethyl-2-phenanthrol (IV) by synthesis[10] *via* 1-acetyl-2-methoxyphenanthrene (Va),[11] Huang-Minlon reduction to 1-ethyl-2-methoxyphenanthrene (Vb) and demethylation with pyridine hydrochloride[12] to IV.

The nature of the glycol system of cafestol was recognized at an early stage by pyrolysis[13] of cafestol monoacetate to an aldehyde[14] (now known to be VI) and by glycol cleavage experiments which furnished formaldehyde[9,15] together with a norketone, epoxynorcafestadienone (II). The keto group of the latter was shown to be present in a five-membered ring by application of Blanc's rule[9] and by infrared measurements.[16] The nature of the last unaccounted carbon atom was demonstrated by infrared examination[5] and Kuhn–Roth oxidation[17] of epoxynorcafestadiene (X)[8,17]—both pointing toward the presence of an angular methyl group.

Aside from stereochemical features, the only two structural points which still remain to be defined are the locations of the angular methyl group and of the five-membered ring bearing the glycol function. We shall first consider the former problem since its solution will restrict considerably the possible points of attachment of the cyclopentane ring.

In our first communication[5] where structure I (without the stereochemical implications) was originally advanced, the angular methyl group was

(1) P. Crabbé, S. Burstein and C. Djerassi, Terpenoids. XXXVI, *Bull. soc. chim. Belg.*, **67**, 632 (1958).

(2) Supported in part by the National Cancer Institute (grant No. CY-2919) of the National Institutes of Health, U. S. Public Health Service.

(3) General Foods Corporation postdoctorate research fellow, 1955–1957.

(4) U. S. Public Health Service predoctorate research fellow, 1956–1958.

(5) H. Bendas and C. Djerassi, *Chemistry & Industry*, 1481 (1955).

(6) C. Djerassi, M. Cais and L. A. Mitscher, THIS JOURNAL, **80**, 247 (1958).

(7) A. Wettstein and K. Miescher, *Helv. Chim. Acta*, **26**, 788 (1943). Nuclear magnetic evidence bearing on this point has been published recently by E. J. Corey, G. Slomp, S. Dev, S. Tobinaga and E. R. Glazier, THIS JOURNAL, **80**, 1204 (1958).

(8) C. Djerassi, H. Bendas and P. Sengupta, *J. Org. Chem.*, **20**, 1046 (1955).

(9) A. Wettstein, H. Fritzsche, F. Hunziker and K. Miescher, *Helv. Chim. Acta*, **24**, 332E (1941).

(10) The experimental details are given in the present paper since the results were announced only briefly in our preliminary communication (ref. 5).

(11) E. Mosettig and A. Burger, THIS JOURNAL, **55**, 2981 (1933).

(12) V. Prey, *Ber.*, **74**, 1219 (1941).

(13) K. H. Slotta and K. Neisser, *ibid.*, **71**, 2342 (1938).

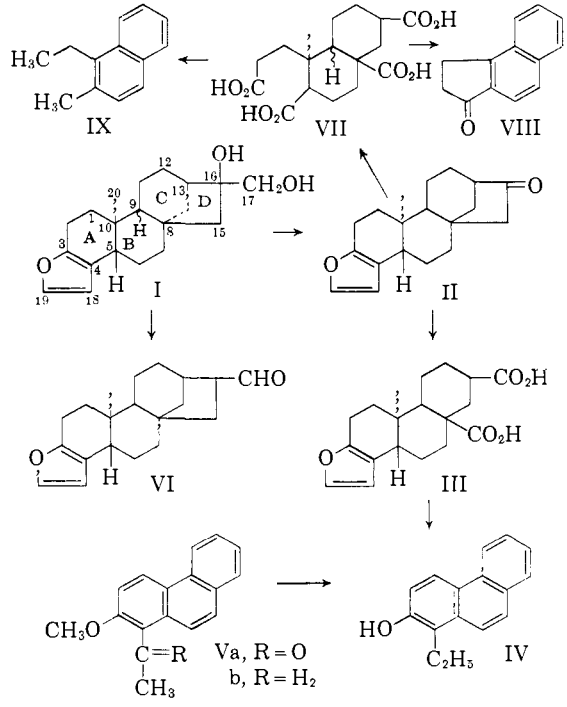
(14) H. Hauptmann and J. Franca, *Z. physiol. Chem.*, **259**, 245 (1939).

(15) H. Hauptmann and J. Franca, THIS JOURNAL, **65**, 81 (1943).

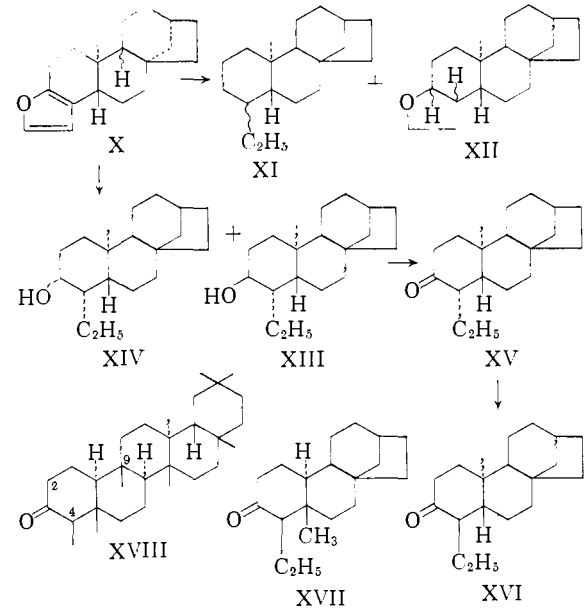
(16) C. Djerassi, E. Wilfred, L. Visco and A. J. Lemin, *J. Org. Chem.*, **18**, 1449 (1953).

(17) R. D. Haworth, A. H. Jubb and J. McKenna, *J. Chem. Soc.*, 1983 (1955).

placed at position 10 by analogy to phyllocladene.[18] As discussed below, the structure of phyllocladene can be considered as settled except for the location of the angular methyl group, which could also have been at C-5 or C-9, C-10 being favored by analogy to the diterpenes of the abietic acid class. Apparently decisive experimental evidence was adduced by Haworth and Johnstone,[19] who transformed epoxynorcafestadienone (II) into the tetracarboxylic acid VII and subjected it to dehydrogenation, whereupon 4,5-benzindan-1-one (VIII) and 1-ethyl-2-methylnaphthalene (IX) were isolated. The formation of these products, notably the naphthalene IX, was interpreted[19] in terms of a cafestol structure in which the angular methyl group was located at C-5 rather than at C-10 (I).[5] Since VIII and IX could also have been produced by a process of methyl migration or by reduction of the carboxyl group (representing C-4 of cafestol) as recently has been observed[20] with certain diterpenoid alkaloids, these dehydrogenation results could still be compatible with our original[5] formulation (I). It was necessary, therefore, to adduce evidence which was free from the ambiguities inherent in high temperature selenium dehydrogenations.



The earlier work of Wettstein and Miescher[21] indicated that the furan ring of cafestol could be opened by hydrogenolysis and it was decided to apply this approach to epoxynorcafestadiene (X), readily obtainable[8,17] by Huang-Minlon reduction of epoxynorcafestadienone (II). The reduction was performed with platinum oxide in acetic acid solution and the complex reaction mixture was separated by careful chromatography. The first three products eluted from the column were the hydrocarbon XI and two isomeric tetrahydrofurans (XII) which were not investigated further. Continued elution produced two isomeric alcohols XIII and XIV, whose stereochemistry will be considered below. Oxidation of the more abundant alcohol XIII afforded an oily ketone (convertible to an analytically pure 2,4-dinitrophenylhydrazone of wide melting point range) which is believed to possess structure XV with an axial ethyl group, since passage over alkaline alumina transformed it in high yield into a crystalline isomer XVI (equatorial ethyl group) characterized by a sharp-melting 2,4-dinitrophenylhydrazone. This ketone XVI represented the key intermediate for our subsequent investigations and it should be noted that on the basis of Haworth and Johnstone's cafestol structure,[19] it would have to be formulated as XVII. The crucial difference between these two alternatives is that XVI should resemble an α-alkylcholestan-3-one while XVII—with an axial methyl group beta to the ketone—should behave in a manner similar to friedelin (XVIII).

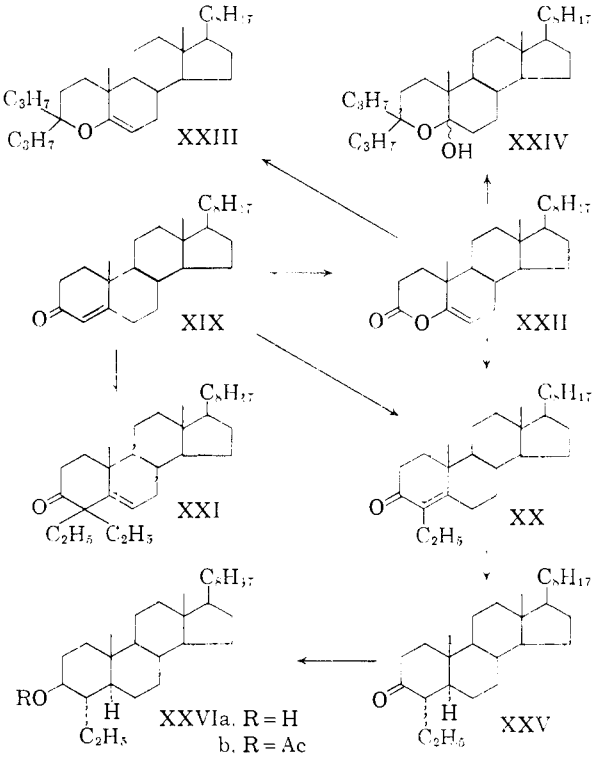


In order to have an adequate model of known stereochemistry, 4α-ethylcholestan-3-one (XXV) was prepared by lithium–liquid ammonia reduction[22] of 4-ethyl-Δ^4-cholesten-3-one (XX). The latter compound was synthesized by two different procedures: (a) direct alkylation[23] of Δ^4-cholesten-3-one (XIX) with ethyl iodide, the companion product, 4,4-diethyl-Δ^5-cholesten-3-one (XXI), being separated by chromatography; (b) treatment of the enol lactone XXII[24] with *n*-

(18) C. W. Brandt, *New Zealand J. Sci. Technol.*, **34B**, 46 (1952).
(19) R. D. Haworth and R. A. W. Johnstone, *J. Chem. Soc.*, 1492 (1957).
(20) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, THIS JOURNAL, **76**, 6068 (1954).
(21) A. Wettstein and K. Miescher, *Helv. Chim. Acta*, **25**, 718 (1942).
(22) 4α-Methylcholestan-3-one was prepared by a similar route (G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956); J. L. Beton, T. G. Halsall, E. R. H. Jones and P. C. Phillips, *ibid.*, 753 (1957); Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958)).
(23) N. A. Atwater, *ibid.*, **79**, 5315 (1957).
(24) R. B. Turner, *ibid.*, **72**, 579 (1950).

propylmagnesium bromide followed by ring closure with alkali. Just as with the corresponding lower homolog,[25] two by-products, probably corresponding to structures XXIII and XXIV, were encountered.

Barton[26] has called attention to the fact that in a reactive ketone (*e.g.*, cholestan-3-one) reduction with both lithium aluminum hydride and metal–alcohol (or ammonia) should lead to the thermodynamically more stable product, namely, the equatorial alcohol. In accordance with this postulate, the identical alcohol, 4α-ethylcholestan-3β-ol (XXVIa), was obtained by reducing 4α-ethylcholestan-3-one (XXV) with lithium aluminum hydride or with lithium–liquid ammonia in the presence of some methanol.[27] The equatorial nature of the alcohol was confirmed by the infrared spectrum of the derived acetate XXVIb which exhibited a sharp type A band[28] in the 8 μ region.



When the ketone XVI, derived from cafestol, was subjected to reduction with lithium in liquid ammonia, there was isolated a homogeneous alcohol (XXXIa) whose acetate (XXXIb) again exhibited a type A band,[28] typical of equatorial alcohols. The same alcohol was also the predominant product (70% yield) when the reduction was performed with lithium aluminum hydride, only a trace of a second alcohol being formed which we believe to be the axial epimer XXXII. It should be recalled that under similar conditions, lithium aluminum hydride reduction of friedelin (XVIII) affords in high yield the axial alcohol, epifriedelanol.[29] Since the ketone XVI from cafestol upon reduction behaves so similarly to 4α-ethylcholestanone (XXV), we feel justified in assigning to it structure XVI with the angular methyl group at C-10. The alternate Haworth–Johnstone[19] expression XVII would be expected to resemble friedelin (XVIII).

As far as the stereochemistry of the various alcohols is concerned, that of 4α-ethylcholestan-3β-ol (XXVIa) follows rigorously from its mode of formation and the infrared spectrum of its acetate (XXVIb); a similar statement with virtually the same degree of certainty can also be made with respect to the alcohol XXXIa of the cafestol series. In order to obtain independent support as well as assign relative configurations to the other alcohols (XIII, XIV, XXXII and LX), resort was taken to the elegant micro-oxidation procedure of Schreiber and Eschenmoser[30] where the rate of oxidation of certain cyclohexanols has been related with considerable precision to the orientation of the alcohol (axial faster than equatorial) as well as to the presence and orientation of alkyl groups alpha and beta to the alcoholic function, the apparent release in strain of the resulting ketone speeding the rate of oxidation. The relevant rate data[31] together with certain model alcohols, are listed in Table I and

TABLE I

RELATIVE RATES OF OXIDATION OF ALCOHOLS

Alcohol	Half-time, min.[a]
4α-Ethylcholestan-3β-ol (XXVIa)	~14.5
Alcohol LX	~16.5
Alcohol XXXIa	~16.5
Alcohol XXXII	~ 4.5
Alcohol XIV	~ 9
Alcohol XIII	~ 6.5
Comparison alcohols[30,31]	
Cholestan-3β-ol	~46
Cholestan-3α-ol	~12
2α-Methylcholestan-3β-ol	~35
2α-Methylcholestan-3α-ol	~ 7

[a] The oxidations were performed at 20.0° as described in ref. 30 with 1.38 mg. of alcohol in 90% acetic acid and 2 equivalents of chromium trioxide; almost exactly one equivalent of reagent was consumed in each case.

are offered in support of the assigned orientations of the alcohols reported in this paper. A particularly important comparison is that of the axial alcohol XXXII *vs.* the equatorial isomer XXXIa, the former being oxidized about 3.5 times faster as is also the case with the model pair (Table I) of 2α-methylcholestan-3α-ol *vs.* 3β-ol. If the angular methyl group were located at position 5, then it would be expected[30] that the axial alcohol XXXII would be oxidized 10–20 times faster than the equatorial one.

(25) F. Sondheimer and Y. Mazur, THIS JOURNAL, **79**, 2906 (1957).

(26) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); see also W. Hückel, M. Maier, E. Jordon and W. Seeger, *Ann.*, **616**, 46 (1958).

(27) This reaction was performed most conveniently directly on 4-ethyl-Δ^4-cholesten-3-one (XX), the double bond and the carbonyl group being reduced in one step (see F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953)).

(28) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *ibid.*, **73**, 3215 (1951).

(29) G. Brownlie, F. S. Spring, R. Stevenson and W. S. Strachan, *J. Chem. Soc.*, 2419 (1956); S. L. Courtney, R. M. Gascoigne and A. Z. Szumer, *ibid.*, 2119 (1956).

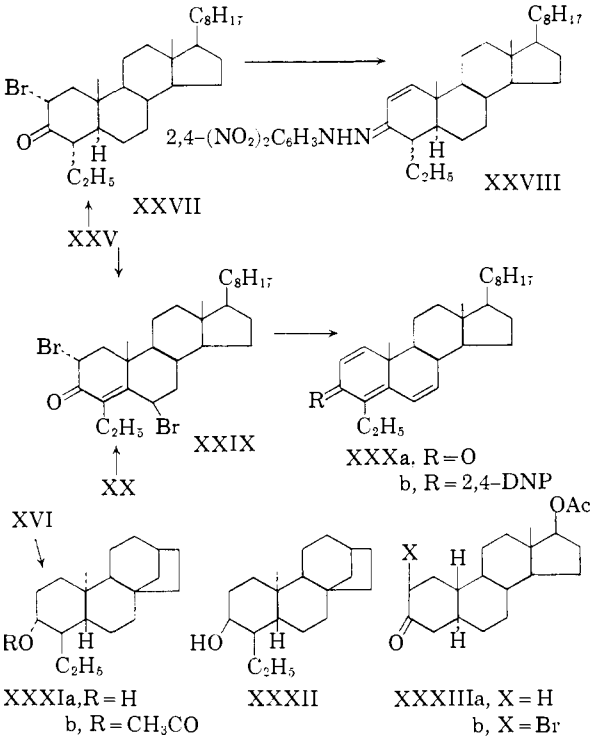
(30) J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955); see also *ibid.*, **40**, 1391 (1957).

(31) We are greatly indebted to Dr. J. Schreiber and Dr. A. Eschenmoser (E.T.H., Zurich) for these measurements.

Additional and conclusive support could be obtained from bromination experiments. Turning first to the model ketone 4α-ethylcholestan-3-one (XXV), monobromination led to the equatorial bromo ketone, 2α-bromo-4α-ethylcholestan-3-one (XXVII), the position of the bromine atom being established by dehydrobromination with 2,4-dinitrophenylhydrazine. The reaction proceeded as described[32] for 2α-bromocholestan-3-one except that a longer reaction time was required, and furnished a 2,4-dinitrophenylhydrazine with $\lambda_{max}^{CHCl_3}$ 381 mμ, typical[33] of steroidal Δ¹-3-keto steroids.

Polybromination of 4α-ethylcholestan-3-one (XXV) followed the same complicated course which had already been encountered earlier[34] with a 4α-methyl-3-keto-5α-steroid. Thus tribromination led to an oily dibromo ketone, which was not purified, but which could also be obtained by dibromination of 4-ethyl-Δ⁴-cholesten-3-one (XX) in ether–acetic acid solution. The latter reaction—in the case of Δ⁴-3-keto steroids—is known[35] to yield 2,6-dibromo-Δ⁴-3-ketones and the completely analogous course coupled with the characteristic[34] ultraviolet absorption maximum at 265 mμ requires that the crude dibromo ketone XXIX be largely 2α,6β-dibromo-4-ethyl-Δ⁴-cholesten-3-one (XXIX). Its formation from the saturated 4α-ethylcholestan-3-one (XXV) can be rationalized readily by assuming spontaneous dehydrobromination of an intermediate 4-bromo derivative, followed by allylic bromination at C-6. Experimental evidence for such dehydrobrominations will be presented below in the cafestol series. The structure of the unsaturated dibromoketone XXIX was confirmed by dehydrobromination with lithium carbonate and lithium bromide in dimethylformamide[36] which furnished an oily trienone (XXXa), characterized as the 2,4-dinitrophenylhydrazone XXXb ($\lambda_{max}^{CHCl_3}$ 410 mμ). The trienone XXXa exhibited ultraviolet absorption maxima at 227 and 305 mμ with an inflection at 259 mμ, in good agreement with the characteristic triple maxima at 222, 256 and 298 mμ observed[35] with steroidal 1,4,6-trien-3-ones lacking a substituent at position 4.

The formation of an equatorial 2α-bromo derivative XXVII in the monobromination of 4α-ethylcholestan-3-one (XXV) is consistent with Corey's generalizations[37] in the steroid series[38] that an equatorial bromo ketone is more stable than the corresponding axial bromo isomer, if in the latter there is present a serious diaxial interaction (bromine–methyl as in XXVII). Conversely, in the absence of such non-bonded interaction, the axial isomer is preferred and the orientation of the bromine atom can be determined readily by ultraviolet,[39] infrared[40] or rotatory dispersion[41] measurements. Thus monobromination[42] of friedelin (XVIII) at positions 2 or 4—where no diaxial interactions exist with a methyl group in the β-position—affords in each case the axial monobromo friedelin. As a further example, we have examined the monobromination of 19-nordihydrotestosterone acetate (XXXIIIa) and found it to yield the predicted[37] axial 2β-bromo ketone XXXIIIb; the location of the bromine atom was confirmed by dehydrobromination to the Δ¹-3-ketone.

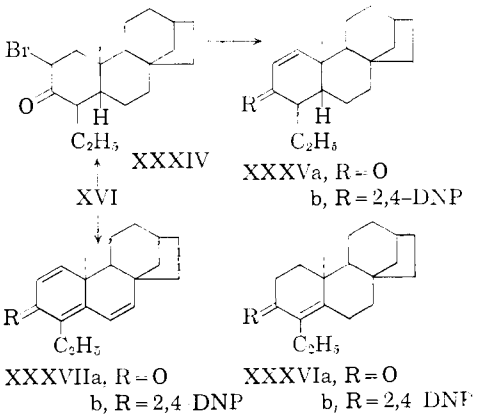


With the above information at hand, it was felt that analogous mono- and tribromination experiments in the cafestol series would be decisive in establishing the site of the angular methyl group. Monobromination of the ketone XVI in glacial acetic acid furnished in good yield a crystalline monobromo derivative, whose equatorial orientation could be demonstrated by all three physicochemical criteria available.[39-41] As pointed out above, such an observation is only consistent with the structural and stereochemical environment shown in structure XVI and inconsistent with the alternative expression XVII possessing an angular methyl group at C-5. In order to establish the position of the bromine atom, the bromoketone XXXIV was treated with 2,4-dinitrophenylhydrazine under standard conditions[32] which worked satisfactorily with the model 2α-bromo-4α-ethylcholestan-3-one (XXVII). Essentially no dehydrobromination was observed—a behavior remi-

(32) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).
(33) C. Djerassi and E. Ryan, *ibid.*, **71**, 1000 (1949).
(34) C. Djerassi and S. Burstein, *ibid.*, **80**, 2593 (1958).
(35) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950).
(36) *Cf.* R. Joly and J. Warnant, *Bull. soc. chim. France*, 367 (1958).
(37) E. J. Corey, THIS JOURNAL, **76**, 175 (1954).
(38) The situation is considerably more complicated in conformationally-mobile, monocyclic cyclohexanones (J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958); C. Djerassi and L. E. Geller, *ibid.*, **3**, 319 (1958)).
(39) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).
(40) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); R. N. Jones, *ibid.*, **75**, 4839 (1953).
(41) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).
(42) E. J. Corey and J. J. Ursprung, *ibid.*, **78**, 5041 (1956).

niscent of 2α-bromofriedelin[42,43] —and a similar resistance was noted upon treatment with γ-collidine; further comment on this point is made below in connection with a discussion of the B/C ring juncture. Dehydrobromination with lithium carbonate and lithium bromide[36] did, however, yield the expected Δ^1-3-ketone XXXVa (λ_{max}^{EtOH} 231 mμ; DNP XXXVb, $\lambda_{max}^{CHCl_3}$ 381 mμ) accompanied by some of the Δ^4-3-ketone XXXVIa. The isolation of the Δ^1-3-ketone XXXVa confirms structure XXXIV for the bromoketone and as shown in the Experimental section, formation of the Δ^4-isomer XXXVIa is due to the lability of the 2-bromo ketone XXXIV, which undergoes rearrangement and partial elimination on heating in acetic acid. The location of the bromine atom at C-2 coupled with the shape of the rotatory dispersion curve (*vide infra*) of XVI establishes the A/B *trans* ring juncture of XVI and *ipso facto* of cafestol (I) itself.

When the ketone XVI was subjected to the tribromination conditions used earlier and the crude bromo compound dehydrobrominated with lithium carbonate and lithium bromide,[36] there was obtained an oily trienone to which is assigned structure XXXVIIa since it exhibited the typical triple ultraviolet absorption maxima at 232, 256 and 302.5 mμ associated with the 1,4,6-trien-3-one chromophore. Furthermore, its crystalline dark-red 2,4-dinitrophenylhydrazone XXXVIIb possessed an absorption maximum at 410 mμ as was observed already above with the steroid model XXXb. The formation of such a trienone is only possible if the angular methyl group is located at C-10 (preventing aromatization to a phenol) and a hydrogen atom is present at C-5.



With the structure and relative stereochemistry of rings A and B solved, the placement of the five-membered ring containing the glycol grouping is simplified considerably. In experiments designed to elucidate the size of ring D, Wettstein and Miescher[44] noted that the carboxyl groups of the dibasic acid (III with furan ring saturated) derived from epoxynorcafestanone (II with furan ring reduced) differed greatly in their reactivity. In fact, the resistance of one of the carboxyl groups in the form of its methyl ester toward saponification was only consistent with its location at a ring juncture and model experiments in the steroid series were performed[44] to support this supposition. It follows, therefore, that the five-membered ring had to originate at one of the angular positions, while the other point of attachment had to be at one of the ring carbons.[45] The above bromination–dehydrobromination experiments eliminate immediately C-5 (hydrogen atom) as well as C-6, C-7 and C-10[46] as points of attachment, there remaining theoretically only four possibilities (8–13, 8–11, 9–12 and 9–14). Direct chemical evidence bearing on this point is scarce and pertains largely to the location of the glycol grouping on the five-membered ring. Using structure I (8–13 attachment of cyclopentane ring to the perhydrophenanthrene skeleton), then it can be seen that the glycol moiety could be placed either next (position 15) to the quaternary carbon atom or two carbon atoms removed (position 16). Bromination experiments have yielded equivocal results:

In our hands[10] bromination of epoxynorcafestanone (II with tetrahydrofuran ring) led to a crystalline monobromo derivative which was resistant to dehydrobromination with γ-collidine. This result is, of course, consistent with a carbonyl group either at C-15 or C-16 since dehydrobromination would be impossible (absence of β-hydrogen atom or violation of Bredt's rule). Haworth and collaborators[17] report that exhaustive bromination of the same ketone led to a tribromo derivative, which seems incompatible with any structure based on I or II since the substance would have to be formulated as the 13,15,15-tribromo-16-ketone—the intermediate $\Delta^{13(16)}$-enol violating Bredt's rule. A possible explanation of Haworth's results is that the third bromine atom entered elsewhere in the molecule, possibly by reaction with the ether linkage. In order to investigate the number of replaceable hydrogen atoms adjacent to the ketone in epoxynorcafestadienone (II), an exchange reaction with sodium deuteride in deuterioethanol was performed whereupon incorporation of two deuterium atoms was noted. As indicated above, this is consistent with structure II, deuterium entering at position 15, while entry at the bridge head (C-13) is impossible since the enol would violate Bredt's rule. The only observation which appears to be helpful in making a decision is the reported[7] inability of epoxynorcafestadienone (II) to undergo condensation with aromatic aldehydes. This resistance is of steric origin since condensation with ethyl formate can be effected[16] and would be much more understandable if the methylene group were located at C-15[47] and the carbonyl group at C-16 as in II.

At this stage, resort was taken to the rotatory dispersion approach[48] by utilizing the nor-ketone

(43) 2α-Bromofriedelin was treated by us with 2,4-dinitrophenylhydrazine under the same conditions.

(44) A. Wettstein and K. Miescher, *Helv. Chim. Acta*, **26**, 631 (1943).

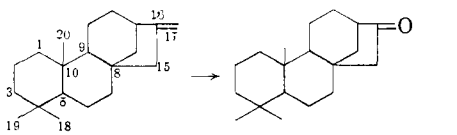
(45) The differential reactivity of the two carboxyl groups did not permit construction of the five-membered ring by two quaternary carbon atoms (*e.g.*, attachment at 9–10 or 8–9).

(46) If any of these carbon atoms were involved, then the trienone XXXVII would violate Bredt's rule.

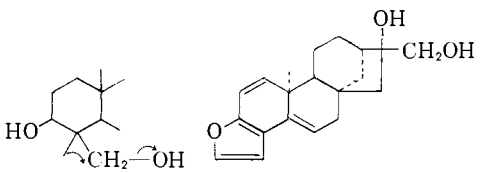
(47) Hindrance would be particularly pronounced if cafestol possesses a 9α-hydrogen atom since C-15 would then be largely shielded by a cage structure (see LV).

(48) See C. Djerassi, *Bull. soc. chim. France*, 741 (1957), for leading references.

XXXIX derived from phyllocladene (XXXVIII),[18] the only uncertainty (aside from stereochemical points) being the location of the angular methyl group and perhaps one of the *gem*-methyl substituents. The rotatory dispersion curve of this nor-ketone XXXIX was so strikingly similar[49] to that of epoxynorcafestanone (II with furan ring reduced) that we consider this as strong, circumstantial evidence that the cyclopentane ring of cafestol is attached at positions 8 and 13. The correctness of this proposal is strengthened further if one considers the biogenetic likeliness that cafestol arises by a similar path to that occurring with phyllocladene (XXXVIII) and the *Garrya* alkaloids[20,50,51] (*e.g.*, LI), substances in which the nature of the carbon skeleton has been proved rigorously. The generation of the furan ring can be visualized readily by assuming a Wagner–Meerwein rearrangement—experimentally demonstrable[52] in the diterpene series—in a precursor such as XL, subsequent ring closure being unexceptional. Aside from the furan ring, cafestol (I) then fits structurally and biogenetically[53] into a class which includes not only the phyllocladene diterpenes but also a number of diterpenoid alkaloids. The stereochemical implications of such a conclusion will be discussed below. It should be noted that, on the basis of structure I for cafestol, the companion kahweol[44] can only be attributed the formulation XLI.



XXXVIII XXXIX



XL XLI

Absolute Configuration of Cafestol and Related Diterpenoids.—The key substance in the structure proof of cafestol was the ketone XVI. The rotatory dispersion curve[49] of its homolog LIX (*vide infra*) was characterized by a negative Cotton effect curve, which was antipodal to the positive one exhibited[54] by 4α-ethylcholestan-3-one (XXV), and the same statement (see Experimental) applies also to XVI. The identical antipodal relationship also was observed in the rotatory dispersion curves (see Experimental) of 2α-bromo-4α-ethylcholestan-3-one (XXVII) and the bromo ketone XXXIV of the cafestol series. Unpublished experiments in our laboratory have already demonstrated that in *saturated* 3-keto steroids, the orientation of C-9 has no effect on the sign of the Cotton effect.[55] Application of the "octant rule"[56] shows that this will almost certainly also be the case irrespective of the stereochemistry at C-8. Combining the rotatory dispersion results with the bromination evidence discussed above which requires an A/B *trans* ring juncture, we can state securely that *cafestol must have the absolute configuration at C-5 and C-10 shown in I* and that this is antipodal to the steroids and diterpenes of the abietic acid group. Further confirmation of this view is presented in Fig. 1 which contains the rotatory dispersion curves of 4-ethyl-1,4,6-cholestatrien-3-one (XXXa) and of the cafestol trienone XXXVIIa, and which are again completely antipodal in nature.

We should now like to turn to a consideration of the relative and absolute configurations in the areas of the B, C and D rings. It was noted above and published earlier[49] that the coincidence (same shape and sign of Cotton effect and virtually identical amplitude) of the rotatory dispersion curves of the nor-ketones XXXIX and II of the phyllocladene (XXXVIII) and cafestol (I) series made it appear very likely that the stereochemical environment in rings C and D, and probably also B, is identical. It has now been possible to measure the rotatory dispersion curve of the keto acid[57] (XLII–XLIX), obtained by degradation of phyllocladene (XXXVIII), and with the exception of the location of the angular methyl and one of the *gem*-methyl groups, its structure but not its stereochemistry is secure. Its rotatory dispersion (Fig. 1) is characterized by a positive Cotton effect curve and since this represents the first substance in this series of diterpenoids where information on the B/C/D junctures can be ascertained, a detailed discussion of its rotatory dispersion curve is in order.

Eight enantiomers (XLII–XLIX) are possible for the keto acid and an analysis of its rotatory dispersion curve *is based on the premise that an angular carboxyl group can be equated to an angular methyl group*.[58] Two approaches can be used to predict the sign of the Cotton effect of the eight enantiomers. The first[49] is an empirical one which compares the unknown ketone with appropriate steroid models. Thus XLII can be written as XLIIa which resembles a 3-keto-5β-steroid and since such ketones exhibit a negative Cotton effect,[59] this would also be predicted for XLII.

(49) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6362 (1956).

(50) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

(51) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, THIS JOURNAL, **77**, 4801, 6633 (1955).

(52) For references see D. H. R. Barton, *Quart. Rev.*, **3**, 36 (1949).

(53) E. Wenkert, *Chemistry & Industry*, 282 (1955), has already outlined the common origin of rings C and D in these diterpenes and alkaloids.

(54) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, THIS JOURNAL, **80**, 4001 (1958).

(55) For instance, both 9α- and 9β-ergostan-3-one are characterized by a single positive Cotton effect of very similar amplitude.

(56) C. Djerassi, W. Klyne, W. Moffitt, A. Moscowitz and R. B. Woodward, in preparation. The "octant rule" offers a means of predicting the sign of the rotatory dispersion Cotton effect in cyclohexanones.

(57) We are greatly indebted to Prof. L. H. Briggs, Auckland University College, New Zealand, for this specimen prepared in his laboratory.

(58) Earlier work from this Laboratory (ref. 49 and C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6377 (1956)) has shown that angular hydrogen, hydroxyl or methyl produces the same effect. The only substance with an angular carbomethoxy group which has been measured is methyl machaerate (C. Djerassi and A. E. Lippman, *ibid.*, **77**, 1825 (1955)) and its negative Cotton effect curve (unpublished observation) is in accordance with expectation.

(59) C. Djerassi and W. Closson, *ibid.*, **78**, 3761 (1956). The angular methyl group and the angular hydrogen atom can be inter-

A similar analysis with XLIII (= XLIIIa) would lead to the prediction of a positive Cotton effect as has been noted with 3-keto-5α-steroids, but considerable ambiguity would arise in employing this approach with the two enantiomers XLIV and XLV. The octant approach[56] does not suffer from this limitation and the predicted sign for the Cotton effect of the four enantiomers XLII–XLV, and hence of their antipodes (XLVI–XLIX), is listed under the structural formulas.[60] Since the observed Cotton effect (Fig. 1) was positive, we

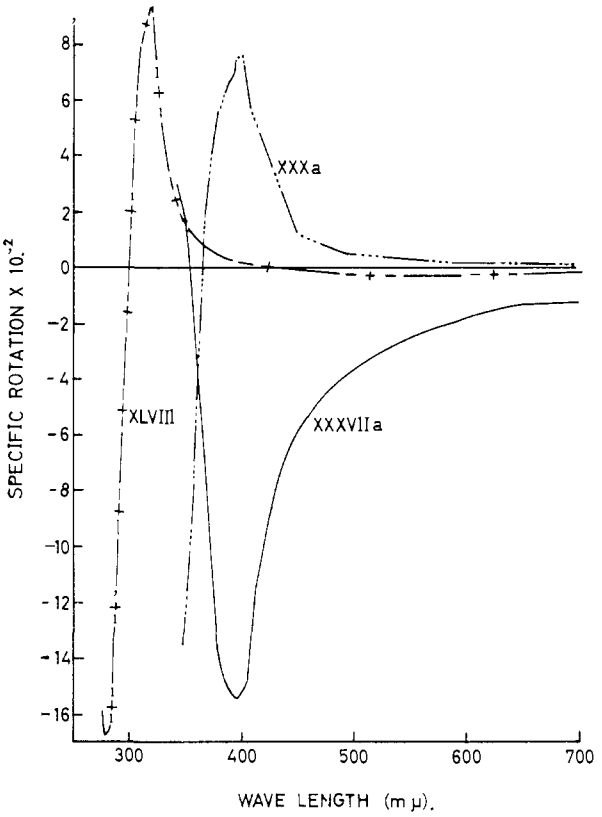
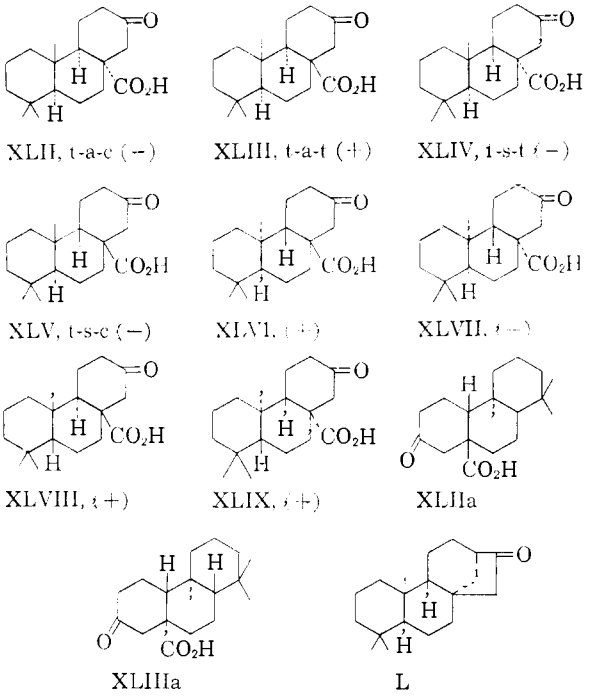


Fig. 1.—Optical rotatory dispersion curves of 4-ethyl-1,4,6-cholestatrien-3-one (XXXa) (in methanol), trienone XXXVIIa (in dioxane) and ketoacid XLVIII derived from phyllocladene (in dioxane).

can reduce the possible representations to four (XLIII,[61] XLVI, XLVIII and XLIX). Of these, XLIX has the angular carboxyl group equatorial to ring C and construction of the five-membered ring



of phyllocladene is possible only if ring C exists as a boat.

In one of our earlier papers[19] we reported on the rotatory dispersion of a variety of *Garrya* alkaloids of the cuauchichicine series[51] and it was noted that F-dihydrocuauchichicine (LI) exhibited a negative Cotton effect curve. Since the carbonyl group in this alkaloid is at C-15 (cafestol numbering system) rather than at C-16 (as in II), the rotatory dispersion curves[19] of II and LI might be expected to be of antipodal type *if their absolute configurations in the relevant regions of the molecule are identical.* Indirect support for this supposition has now been presented in the atisine series (LII) where a multistage degradation to the phenol LIII has been performed.[62] Its rotation was found to be strongly negative, in contrast to the positive one of ring C phenols of the dehydroabietic acid class. Consequently, Dvornik and Edwards[62] suggested that the phenol should be assigned the absolute configuration LIII—antipodal to that of the abietic acid class but identical with that of cafestol (I)—and coupled with earlier stereochemical conclusions[50,51] in the related *Garrya* alkaloids, this was expanded to LII for atisine itself. The close biogenetic relationship of the *Garrya* alkaloids, the atisine group and the phyllocladene diterpenes (including cafestol) can be considered as extremely likely.[53] The relative configuration in the *Garrya* alkaloids at C-9 has been assumed to be opposite to that of the C-10 angular substituent and we shall comment on this point below. There exists, however, good evidence[50] that the five-membered D ring is pointed away from the basic nitrogen atom and that the 8–15 bond (see numbering in LI) and hence also the 13–16 bond are opposite to the angular substituent attached to C-10.

changed without affecting the Cotton effect (H. Aebli, C. A. Grob and E. Schumacher, *Helv. Chim. Acta*, **41**, 779, Fig. 1 (1958)).

(60) It should be noted that the *trans-syn-trans* enantiomer XLIV and its antipode XLVIII cannot exist in an all-chair conformation and that ring B must be a boat (see W. S. Johnson, *Experientia*, **7**, 315 (1951)).

(61) It should be noted that of the four possible representations, only one—XLIII—has the A/B absolute configuration of the abietic acid diterpenes (see W. Klyne, *J. Chem. Soc.*, 3072 (1953)). If this were correct, then the derived nor-ketone (XXXIX) would be represented by L and *it is conceivable that its rotatory dispersion curve could still be virtually identical (as was shown to be the case*[19]*) with that of epoxy-norcafestanone (II with tetrahydrofuran ring), provided the latter possesses a 9α-hydrogen atom.* This uncertainty—cafestol (I) and phyllocladene (XXXVIII) being antipodal in ring A but possessing identical absolute configuration in rings B, C and D—cannot be settled definitely at this time by means of rotatory dispersion, since not enough information is available on the effect of remote rings upon the rotatory dispersion of a fused cyclopentanone system as is present in II and XXXIX.

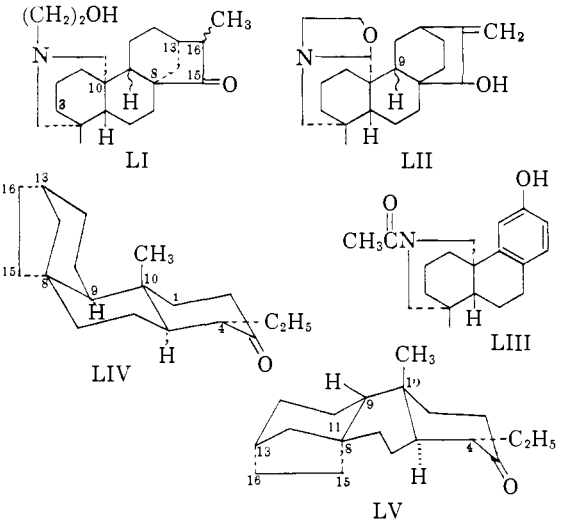
(62) D. Dvornik and O. E. Edwards, *Chemistry & Industry*, 823 (1958).

If we now make the attractive, though speculative,[63] assumption that all of the phyllocladene diterpenes and alkaloids possess the same stereochemical feature[61] and we examine the four enantiomeric forms XLIII, XLVI, XLVIII and XLIX which are consistent with our rotatory dispersion results, then it will be observed that only two of them—XLVI and XLVIII—satisfy the observed relative stereochemical requirement of the *Garrya* alkaloids.[50] *A priori*, an *anti* backbone as in XLVI would appear more reasonable on grounds of analogy to the abietic acid series, but it should be noted that diterpenoids with a *syn* relationship at C-9 and C-10 are also known.[64]

As far as the stereochemistry of C-9 is concerned, there exist some indications in derivatives of cafestol that the correct representation may be I with a 9α-orientation, *i.e.* a *syn* backbone. If we rewrite the ketone XVI derived from cafestol in conformational representations consistent with XLVI and XLVIII, then structures LIV or LV are obtained. It will be recalled that one difference in the behavior of the ketone XVI and the corresponding steroid model 4α-ethylcholestan-3-one (XXV) was the increased resistance of the 2-bromocafestol ketone XXXIV toward dehydrobromination. A similar resistance has been observed[42,43] in 2α-bromofriedelin and has been ascribed[42] to the axial 9β-methyl group in XVIII which hinders removal of a proton at C-1. Turning now to the conformational representations LIV and LV, it will be noted that in LIV, rings A and B possess the same conformation as the steroid model XXVII and no major difference should be anticipated. In LV, however, ring B has to exist as a boat and the 9–11 bond now acquires a quasi-axial character, similar to the 9β-methyl group in friedelin (XVIII) and resistance toward dehydrobromination can, therefore, be expected. Furthermore, the slight, but significant, differences in the ultraviolet absorption spectra of the trienones XXXa and XXXVIIa might be due to the presence of a *syn* backbone in cafestol and the difficulty in effecting condensation at C-15 in epoxynorcafestadienone (II) is also more understandable in a structure based on LV.[47]

Another circumstantial argument in favor of a *syn* arrangement at C-9 and C-10 can be presented from the earlier literature. Wettstein, *et al.*,[65] as well as Haworth and collaborators[17,19] have drawn attention to the fact that in dicarboxylic and tetracarboxylic acids derived from opening of ring A of cafestol (*e.g.*, VII), the carboxyl group originating from C-4 exhibits considerable hindrance in so far as saponification of its ester is concerned, although it can be esterified with alcohols and mineral acid (in contrast to the carboxyl group—*e.g.*, III—derived from C-15). If cafestol is based on conformation LV, then opening of ring A will now permit conversion of ring B from a boat to a chair, a consequence of this change being the conversion of the (equatorial) carboxyl group corresponding to C-4 into an axial one. Such a change would be consistent with the observed degree of hindrance.

In summary, there seems to be no doubt about the antipodal stereochemistry of cafestol (I) in so far as ring A is concerned. Whether this applies to phyllocladene[61] *and the diterpenoid alkaloids cannot be said with the same degree of assurance although the circumstantial evidence—rotatory dispersion of the keto acid XLVI (or XLVIII) and the rotation*[62] *of the phenol LIII—points in this direction.* The orientation of C-9 is not established, but a *syn* backbone seems more likely in the cafestol series (I with 9α-hydrogen).



An important achievement, which would put these suggestions on a firm basis, would be an experimental interconversion of cafestol (whose absolute configuration at C-5 and C-10 is known) with a diterpene of the phyllocladene class. The obvious candidate would be isosteviol,[66] which probably has structure LVI and which exhibits[49] a very strong negative Cotton effect. The amplitude of its dispersion curve is much greater than that of LI which may only be a reflection of the structural differences in the rest of the molecule or may actually represent stereochemical or even skeletal aberrations. In an attempt to settle this point, the aldehyde VI was reduced by the Huang-Minlon procedure to epoxycafestadiene (LVII) and then subjected to platinum oxide–acetic acid hydrogenolysis. The alcohol isolated from the hydrogenation is assigned structure LVIII since oxidation, just as with the lower homolog XIII, afforded an oily ketone, which was transformed into a crystalline one upon passage over alkaline alumina. The crystalline ketone is represented as LIX, with an equatorial ethyl function, since it is stable to hot alkali and is transformed upon lithium aluminum hydride reduction to an alcohol formulated as LX by analogy to the reduction of XVI to XXXIa, as well as on the basis of the quantitative oxidation results (Table I).[30,31] The

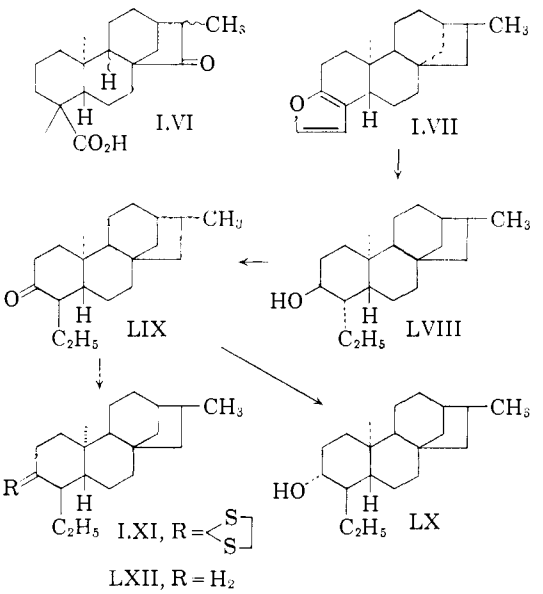
(63) See, however, E. Wenkert and J. W. Chamberlin, THIS JOURNAL, **80**, 2912 (1958).

(64) B. Green, A. Harris, W. B. Whalley and H. Smith, *Chemistry & Industry*, 1369 (1958); H. H. Bruun, R. Ryhage and E. Stenhagen, *Acta Chem. Scand.*, **12**, 789 (1958); B. Green, A. Harris and W. B. Whalley, *J. Chem. Soc.*, 4715 (1958).

(65) A. Wettstein, F. Hunziker and K. Miescher, *Helv. Chim. Acta*, **26**, 1197 (1943).

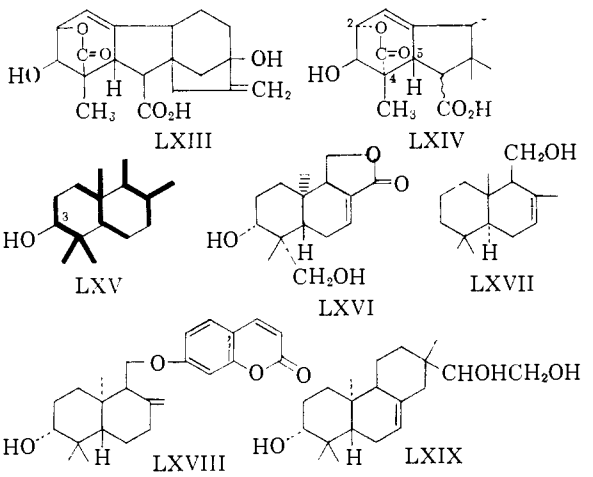
(66) E. Mosettig and W. R. Nes, *J. Org. Chem.*, **20**, 884 (1955).

ketone LIX, whose negative rotatory dispersion Cotton effect already has been reproduced,[49] was transformed into the thioketal LXI and thence by Raney nickel desulfurization into the crystalline hydrocarbon LXII. It was hoped that this hydrocarbon or an isomer thereof could be obtained from isosteviol (LVI) by removal of the keto group, lithium aluminum hydride reduction, followed by dehydration with Wagner–Meerwein rearrangement and reduction. Unfortunately, the sequence failed at the penultimate stage[67] and an interconversion between cafestol and another diterpenoid still remains to be realized.



The above discussion of the absolute configuration of cafestol and related diterpenes has a very definite bearing[68] on the absolute configuration of gibberellic acid. Its structure LXIII (no stereochemical connotations) has been established by Cross, *et al.*,[69] and its biogenetic relationship to phyllocladene (XXXVIII)—already apparent on structural grounds—has been supported recently by tracer experiments.[70] If the above suggestion is correct that phyllocladene (XXXVIII), the diterpenoid alkaloids and cafestol (I) all possess the same absolute configuration, then it follows automatically that gibberellic acid has the absolute configuration at positions 2, 3, 4 and 5 outlined in partial formula LXIV. Even if phyllocladene should not possess the 5β,10α-absolute configuration[61] assigned to cafestol (I), then in our opinion the circumstantial evidence is still in favor of the absolute configuration LXIV for gibberellic acid (LXIII) for several reasons[68]:

The biocyclofarnesol skeleton LXV with a hydroxyl group at C-3 is extremely rare in the sesquiterpene and diterpene field. In fact, among sesquiterpenes until recently there existed only iresin (LXVI)[71] and three of its relatives[3] and these have been shown[34] to have the 5β,10α-absolute configuration depicted in LXVI. Subsequently, there was discovered drimenol (LXVII) which possesses[72] the conventional "steroid" absolute configuration (5α,10β) and farnesiferol A (LXVIII)[73] which again belongs to the iresin series in terms of its absolute configuration. Turning now to diterpenes, the only ones which contain the partial structure LXV are cafestol (I) (in terms of its precursor XL) and darutigenol (LXIX).[74] In other words, every sesqui- and diterpene which has so far been discovered[74a] and which contains an oxygen atom in position 3 of a bicyclofarnesol skeleton such as LXV possesses the "wrong" 5β,10α-absolute configuration. Therefore we should like to suggest that the stereochemical requirements of the enzyme system promoting ring closure of the open chain sesqui- and diterpenoid precursor by OH (mechanistically, though not in terms of absolute configuration, similar to the cyclization of squalene[75] in the triterpene field) are such as to yield the 5β,10α-absolute configuration. Since the biogenetic precursor of gibberellic acid (LXIII) clearly falls within the scope of this definition (LXV), we predict the absolute configuration LXIV for this plant growth factor and it will be interesting to see whether proof of absolute configuration by classical means will bear this out.



(67) Private communication from Dr. E. Mosettig, National Institutes of Health, Bethesda, Md.

(68) First discussed by C. D. at the Chemistry Department Colloquium of Columbia University, May 7, 1958.

(69) B. E. Cross, J. F. Grove, J. MacMillan, T. P. C. Mulholland and N. Sheppard, *Proc. Chem. Soc.*, 221 (1958); B. E. Cross, J. F. Grove, J. MacMillan and T. P. C. Mulholland, *Chemistry & Industry*, 954 (1956).

(70) A. J. Birch, R. W. Rickards and H. Smith, *Proc. Chem. Soc.*, 192 (1958).

(71) C. Djerassi, W. Rittel, A. L. Nussbaum, F. W. Donovan and J. Herran, THIS JOURNAL, **76**, 6410 (1954).

(72) C. J. W. Brooks and K. H. Overton, *Proc. Chem. Soc.*, 322 (1957).

(73) L. Caglioti, H. Naef, D. Arizoni and O. Jeger, *Helv. Chim. Acta*, **41**, 2278 (1918).

(74) J. Pudles, A. Diara and E. Leiserer, *Bull. soc. chim. France*, in press. The position of the angular methyl group has not been settled completely and it could also be located at C-9 rather than at C-10.

(74a) ADDED IN PROOF.—Recently F. E. King, T. J. King and J. M. Uprichard, *J. Chem. Soc.*, 3428 (1958), have established the absolute configuration of cassaine, a diterpenoid which also seems to fall within our definition LXV. Since this substance was shown to have the usual absolute configuration of the steroids, it is probable that our hypothesis has to be refined somewhat based on the complete isoprenoid skeleton of the particular substance. It should be noted that cassaine is based on an isoprenoid pattern which is different from that of the compounds discussed in this paper.

(75) See K. Bloch, *Vitamins and Hormones*, **15**, 119 (1957), and references cited therein.

Experimental[76]

Synthesis[77] of 1-Ethyl-2-phenanthrol (IV).—A mixture of 0.5 g. of 1-acetyl-2-methoxyphenanthrene (Va)[11] (m.p. 175°), 0.25 g. of potassium hydroxide, 3.5 cc. of 98% hydrazine and 20 cc. of diethylene glycol was heated under reflux for 1 hr., the condenser was removed until the temperature of the vapor rose to 195° and refluxing was continued for an additional 4 hr. **1-Ethyl-2-methoxyphenanthrene (Vb)** was isolated by extraction with ether, washing with dilute potassium hydroxide and water, drying, evaporation and recrystallization from heptane; yield 0.34 g., m.p. 142–146° (m.p. 144–146° after high vacuum sublimation).

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.31; H, 6.59.

The above methyl ether Vb (200 mg.) was heated at 210° for 45 min. with 1.0 g. of pyridine hydrochloride,[12] water was added, the precipitate was collected and recrystallized from dilute ethanol. The colorless crystals (m.p. 150–152°) were shown to be identical with **1-ethyl-2-phenanthrol (IV)** derived[8] from cafestol by mixture melting point determination, as well as by coincidence of the ultraviolet[8] spectra and X-ray diffraction patterns.[78]

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.66; H, 6.77.

1-Ethyl-2-phenanthrol 3,5-dinitrobenzoate was prepared in pyridine solution at room temperature (48 hr.) and recrystallized from methyl ethyl ketone, whereupon it exhibited m.p. 249–250°, undepressed on admixture with a specimen obtained[8] by dehydrogenation. The X-ray diffraction patterns[78] were also identical.

Bromination[77] of Epoxynorcafestanone.—A solution of 1.37 g. of epoxynorcafestanone[65] (II with tetrahydrofuran ring) of m.p. 130–131° in 10 cc. of glacial acetic acid was treated dropwise with 12.5 cc. of a solution of 3.0 g. of bromine in 50 cc. of acetic acid. The solution was warmed after addition of the first few drops of bromine solution, but the rest of the addition was conducted at room temperature. After 3 hr., water was added, the bromo ketone was extracted with ether and the gummy residue (1.4 g.) was recrystallized several times from ethanol, whereupon it exhibited m.p. 183–185° (yield 0.65 g.), $[\alpha]_D$ −31°. Identical results were obtained when the bromination mixture was worked up after 5 min.

Anal. Calcd. for $C_{19}H_{27}BrO_2$: C, 62.15; H, 7.41; Br, 21.76. Found: C, 62.26; H, 7.49; Br, 21.81.

No collidine hydrobromide was formed after heating 200 mg. of the bromo ketone with 20 cc. of γ-collidine for 90 min. and unchanged starting material was recovered.

Hydrogenolysis of Epoxynorcafestadiene (X).—Hydrogen uptake, corresponding to 2.82 equivalents, ceased within 2–4 hr. when 4.0 g. of epoxynorcafestadiene (X)[8,17] was hydrogenated at room temperature and atmospheric pressure with 1.60 g. of prereduced platinum oxide catalyst in 250 cc. of glacial acetic acid. After filtration of the catalyst, the acetic acid was removed *in vacuo* and the residue was hydrolyzed by heating under reflux for 1 hr. with 100 cc. of 1% methanolic potassium hydroxide. The product (3.55 g. of oil) was isolated by ether extraction and material (5.0 g.) obtained from two experiments was chromatographed on 150 g. of Alcoa F-20 alumina (alkaline reaction) with the following results.

Elution with 400 cc. of hexane afforded 0.38 g. of a colorless oil, which was distilled at 110° and 0.01 mm. to provide the analytical sample of the **hydrocarbon XI**, $[\alpha]_D$ −71°.

Anal. Calcd. for $C_{19}H_{32}$: C, 87.62; H, 12.38. Found: C, 87.19; H, 12.02.

Change of the development solvent to hexane–benzene (65:35) furnished in the first 600 cc. 1.27 g. of crystals, m.p. 65–70°, which represent one of the stereoisomeric forms of the **tetrahydrofuran XII**, m.p. 72–73° (from acetone), $[\alpha]_D$ −33.5°, no infrared absorption bands in the hydroxyl or carbonyl regions.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02; O, 5.83. Found: C, 82.95; H, 10.91; O, 5.63.

Further washing of the column with the same solvent pair gave in the second 1.2-l. portion 1.22 g. of colorless oil, apparently a stereoisomer of the **tetrahydrofuran XII**, which was distilled at a bath temperature of 120–130° and 0.01 mm.; $[\alpha]_D$ −62°, no infrared hydroxyl or carbonyl absorption.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02; O, 5.83. Found: C, 82.90; H, 11.22; O, 6.11.

Elution with benzene or benzene–ether mixtures gave only negligible amounts of oil, while development of the chromatogram with ether led to the isomeric alcohols XIII and XIV. The first 400 cc. provided 0.90 g. (m.p. 104–114°) of the **alcohol XIII**, raised to m.p. 130–132° (0.72 g.) after recrystallization from hexane, $[\alpha]_D$ −64°.

The axial character of the alcoholic function, already indicated by the oxidation experiments[30,31] summarized in Table I, is supported further by the observation that no acetate was formed upon attempted acetylation with acetic anhydride–pyridine at room temperature overnight.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66; O, 5.79. Found: C, 82.58; H, 11.81; O, 6.07.

The last 600 cc. of ether removed 0.5 g. of oil which crystallized on standing, m.p. 80–98°. Recrystallization from hexane or pentane afforded apparently dimorphic crystals of the **alcohol XIV**, m.p. 94–96° or 104–106°, $[\alpha]_D$ −62°.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66; O, 5.79. Found: C, 81.97; H, 11.64; O, 6.09.

Oxidation of the Alcohol XIII.—To the alcohol XIII (0.45 g.) dissolved in 15 cc. of glacial acetic acid was added at room temperature in portions a solution of 0.17 g. of chromium trioxide in 10 cc. of acetic acid. After standing overnight, it was poured into water, extracted with ether, washed, dried and evaporated. The resulting oil was chromatographed on 8.0 g. of Merck acid-washed alumina. Elution with 450 cc. of hexane–benzene (9:1) afforded 0.38 g. of a colorless oil, $\lambda_{max}^{CHCl_3}$ 5.84 μ; R.D. (*c* 0.16) in methanol: $[\alpha]_{700}$ −60°, $[\alpha]_{589}$ −80°, $[\alpha]_{307.5}$ −766°, $[\alpha]_{275}$ +144°, $[\alpha]_{265}$ 0°.

This ketone is believed to be the isomer XV[79] because of its facile transformation into the crystalline isomer XVI and because it formed readily an analytically pure yellowish-orange **2,4-dinitrophenylhydrazone** (m.p. 140–150°) which even after four recrystallizations from chloroform–ethanol exhibited a wide melting point range (165–185°).

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.05; H, 7.54; N, 12.33. Found: C, 66.58; H, 7.64; N, 12.15.

When a solution of 0.38 g. of the *oily* ketone XV[79] in hexane–benzene (3:2) was passed over 8.0 g. of Alcoa F-20 (basic) alumina, there was obtained 0.36 g. of **crystalline ketone XVI**, m.p. 80–88°, raised to m.p. 86–88° after two recrystallizations from methanol; λ_{max}^{EtOH} 282 mμ, $\lambda_{max}^{CHCl_3}$ 5.84 μ; R.D. (*c* 0.133) in methanol: $[\alpha]_{700}$ −64°, $[\alpha]_{589}$ −88°, $[\alpha]_{307.5}$ −1536°, $[\alpha]_{270}$ +890°, $[\alpha]_{255}$ +562°.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02; O, 5.83. Found: C, 83.42; H, 11.02; O, 5.99.

The crystalline ketone XVI formed a **2,4-dinitrophenylhydrazone**, which crystallized as yellow-orange needles, m.p. 200–202° after a single recrystallization from chloroform–ethanol, in contrast to the wide melting point range of the corresponding derivative of the oily ketone XV. The analytical sample exhibited m.p. 202–203°.

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.05; H, 7.54; N, 12.33. Found: C, 66.27; H, 7.47; N, 12.10.

4-Ethyl-Δ⁴-cholesten-3-one (XX). (a) **By Alkylation of Δ⁴-Cholesten-3-one (XIX).**—A solution of 1.1 cc. of ethyl iodide in 100 cc. of dry *t*-butyl alcohol was added over a period of 2.5 hr. to a refluxing solution of 2.0 g. of Δ⁴-cholesten-3-one (XIX) in 60 cc. of *t*-butyl alcohol containing 0.4 g. of potassium. After heating for one additional hour, 20 cc. of water was added and the solvents were removed *in vacuo*. The residue was leached with hexane and then chromatographed on 100 g. of silica gel (Sargent). Hexane–benzene (8:2) eluted 0.36 g. of **4,4-diethyl-Δ⁵-cholesten-3-**

(76) Melting points were determined on the Kofler block. Unless noted otherwise, rotations were obtained in chloroform solution. We are indebted to Miss B. Bach for the infrared spectroscopic measurements and to Mrs. T. Nakano and Mrs. C. Wilkinson for rotatory dispersion measurements. The microanalyses are due to Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(77) This experiment was performed by the late Dr. Hillel Bendas (see ref. 5).

(78) Performed in the Lilly Research Laboratories, Indianapolis, Ind., through the courtesy of Dr. N. Neuss.

(79) The ketone is probably already contaminated by some of the isomer XVI.

one (XXI),[79a] which was recrystallized from ether–methanol, whereupon it showed m.p. 89–91°, $\lambda_{max}^{CHCl_3}$ 5.80 μ, no selective high ultraviolet absorption.

Anal. Calcd. for $C_{31}H_{52}O \cdot 0.5CH_3OH$: C, 82.93; H, 11.90; O, 5.19. Found: C, 83.23; H, 11.47; O, 5.64.

Further elution with hexane–benzene (1:1) produced an oil (0.88 g.) which solidified on trituration with methanol. Once-crystallized material (m.p. 74–81°, λ_{max}^{EtOH} 251 mμ, log ε 3.92) was re-chromatographed on 50 g. of Woelm alumina, thereupon yielding 0.52 g. of **4-ethyl-Δ⁴-cholesten-3-one (XX)**, m.p. 83–85°, $[\alpha]D$ + 93°, λ_{max}^{EtOH} 251 mμ, log ε 4.14, $\lambda_{max}^{CHCl_3}$ 5.99 and 6.18 μ.

(b) By Reaction of Propylmagnesium Bromide on Enol Lactone XXII.—A solution of propylmagnesium bromide, prepared from 5 cc. of *n*-propyl bromide, 0.14 g. of magnesium turnings and 100 cc. of ether, was added dropwise with stirring at 0° in an atmosphere of nitrogen, to 1.5 g. of the enol lactone XXII[24] in 100 cc. of 1:1 ether–benzene containing 20 mg. of cuprous chloride. The addition required 20 min. and after heating under reflux for 1.5 hr., the mixture was poured onto ice and 50 cc. of 6 *N* hydrochloric acid. The total product, isolated with ether, was heated under reflux for 3 hr. with 2.0 g. of sodium hydroxide, 200 cc. of methanol and 10 cc. of water and then left at room temperature overnight. The solution was concentrated to one-half its original volume, diluted with water and extracted with ether. Acidification of the aqueous layer regenerated 0.43 g. of the keto acid from which the enol lactone XXII had been prepared.

Evaporation of the ether solution yielded 0.82 g. of oil which was chromatographed on 25 g. of Alcoa F-20 alumina. Elution with hexane–benzene (4:1) gave 0.47 g. of **4-ethyl-Δ⁴-cholesten-3-one (XX)**, m.p. 80–87°, raised to 87–89° after recrystallization from methanol. The spectroscopic properties of this specimen were identical with those obtained by procedure (a).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72; O, 3.88. Found: C, 84.20; H, 12.04; O, 4.19.

The dark red **2,4-dinitrophenylhydrazone** crystallized from chloroform–ethanol, m.p. 264–265°, $\lambda_{max}^{CHCl_3}$ 395 mμ, log ε 4.55.

Anal. Calcd. for $C_{35}H_{52}N_4O_4$: C, 70.90; H, 8.84. Found: C, 70.76; H, 8.93.

When the enol lactone was added to the Grignard solution, there was isolated (by hexane elution in the chromatogram) a semi-solid giving a brown color with tetranitromethane and which is probably the enol ether XXIII.[25] The more polar product, m.p. 190–193° (from hexane–benzene), eluted with ether probably has the constitution XXIV.[25]

Anal. Calcd. for $C_{32}H_{58}O_2$: C, 80.95; H, 12.31; O, 6.74. Found: C, 80.44; H, 11.77; O, 7.35.

4α-Ethylcholestan-3-one (XXV).—A solution of 200 mg. of 4-ethyl-Δ⁴-cholesten-3-one (XX) in 25 cc. of dry ether was added dropwise to 150 mg. of lithium in 100 cc. of liquid ammonia. After complete addition, the mixture was stirred for an additional 45 min., excess lithium was destroyed with solid ammonium chloride and the ammonia was allowed to evaporate. The crude product (190 mg., m.p. 105–117°) obtained by extraction with ether was chromatographed on 5 g. of Alcoa alumina (basic) and eluted with hexane–benzene (9:1). Recrystallization from ether–methanol yielded 145 g. of colorless crystals, m.p. 120–122°, $[\alpha]D$ +38°, $\lambda_{max}^{CHCl_3}$ 5.83 μ. The rotatory dispersion curve, characterized by a positive Cotton effect, has already been published.[54]

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.69; H, 11.92.

The 2,4-dinitrophenylhydrazone crystallized from chloroform–ethanol as light orange lustrous plates, m.p. 226–228°, $\lambda_{max}^{CHCl_3}$ 370 mμ, log ε 4.37.

Anal. Calcd. for $C_{35}H_{54}N_4O_4$: C, 70.67; H, 9.15; N, 9.42. Found: C, 70.29; H, 9.53; N, 9.62.

4α-Ethylcholestan-3β-ol (XXVIa). (a) By Lithium Aluminum Hydride Reduction of XXV.—A mixture of 120 mg. of 4α-ethylcholestan-3-one (XXV), 150 mg. of lithium aluminum hydride and 15 cc. of dioxane was heated under reflux for 1 hr., excess reagent was destroyed by the addition of ethyl acetate and, after pouring into water, the product was extracted with methylene dichloride. Chromatography on 5 g. of Alcoa alumina, elution with benzene and recrystallization from pentane led to 85 mg. of the alcohol XXVIa, m.p. 141–143°, $[\alpha]D$ +24°.

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.58; H, 12.58. Found: C, 83.62; H, 12.23.

(b) By Lithium–Ammonia Reduction of XX.—4-Ethyl-Δ⁴-cholesten-3-one (XX) (200 mg.) in 15 cc. of dioxane was added to a solution of 150 mg. of lithium in 50 cc. of liquid ammonia. After stirring for 1 hr., methanol was added until all the lithium had reacted and a new portion of lithium metal was added to maintain the blue color for 1 hr. The reaction mixture was then processed as above to furnish 190 mg. of crystals, m.p. 135–143°; one recrystallization from pentane afforded the alcohol XXVIa, m.p. 140–143°, undepressed on admixture with the specimen prepared according to (a). The infrared spectra (carbon disulfide solution) of the two samples were identical.

The acetate XXVIb, prepared with acetic anhydride–pyridine at room temperature, crystallized from methanol as needles, m.p. 105–107°, $[\alpha]D$ +34°, $\lambda_{max}^{CS_2}$ 5.76 μ and sharp type A band[28] at 8.03 μ.

Anal. Calcd. for $C_{31}H_{54}O_2$: C, 81.16; H, 11.87. Found: C, 80.80; H, 12.04.

2α-Bromo-4α-ethylcholestan-3-one (XXVII).—A solution of 0.30 g. of 4α-ethylcholestan-3-one (XXV) in 50 cc. of glacial acetic acid was treated dropwise at room temperature with 7.2 cc. of a 0.1 *M* solution of bromine in acetic acid. After stirring for 30 min., the solution was poured onto ice, the bromo ketone was extracted with ether and chromatographed in hexane solution on silica gel. Elution with hexane–benzene (4:1) afforded 0.28 g. of XXVII, m.p. 112–114°, $[\alpha]D$ +33°, $\lambda^{EtOH-CHCl_3}$ (3.2:1.8) 295 mμ, log ε 1.93,[80] $\lambda_{max}^{CHCl_3}$ 5.75 μ; R.D. (*c* 0.05) in methanol: $[\alpha]_{589}$ +50°, $[\alpha]_{310}$ +822°, $[\alpha]_{285}$ −306°.

Anal. Calcd. for $C_{29}H_{49}BrO$: C, 70.59; H, 10.01; Br, 16.15; O, 3.25. Found: C, 70.76; H, 9.73; Br, 16.49; O, 3.04.

The position of the bromine atom was established by dehydrobromination of 85 mg. of XXVII with 45 mg. of 2,4-dinitrophenylhydrazine in 1 cc. of acetic acid.[32] The boiling solution was concentrated in a current of nitrogen, the original volume restored by the addition of more acetic acid and the process was repeated three times. The reddish 2,4-dinitrophenylhydrazone was filtered and recrystallized twice from chloroform–ethanol to give rosettes of **4α-ethyl-Δ¹-cholesten-3-one 2,4-dinitrophenylhydrazone (XXVIII)**, m.p. 220–222°, $\lambda_{max}^{CHCl_3}$ 381 mμ,[33] log ε 4.39.

Anal. Calcd. for $C_{35}H_{52}N_4O_4$: C, 70.90; H, 8.84; N, 9.45. Found: C, 71.19; H, 8.73; N, 10.09.

4-Ethyl-1,4,6-cholestatrien-3-one (XXXa). (a) From 4-Ethyl-Δ⁴-cholesten-3-one (XX).—A solution of 0.32 g. of bromine in 9.4 cc. of acetic acid was added dropwise to 0.41 g. of XX dissolved in 40 cc. of dry ether. The reaction was started at ice-bath temperature[35] but since bromine uptake was very slow, it was continued at room temperature. Removal of the solvents *in vacuo*, dilution with water and extraction with ether provided 0.53 g. of the oily 2α,6β-dibromo-Δ⁴-3-ketone XXIX, λ_{max}^{EtOH} 265 mμ, log ε 4.13, which was used directly for the next step. The bromo ketone was dissolved in 15 cc. of redistilled dimethylformamide, heated to 100° and while stirring there was added 0.45 g. of anhydrous lithium carbonate and 0.52 g. of anhydrous lithium bromide. The entire reaction was conducted in an atmosphere of nitrogen and after heating overnight, the **trienone XXXa** was extracted with ether and purified by chromatographing twice on 25 g. of alumina. The resulting product was still an oil, λ_{max}^{EtOH} 227, 259 (infl.) and 305 mμ, log ε 4.22, 3.93 and 4.16; $\lambda_{max}^{CHCl_3}$ 6.00, 6.09 and 6.16 μ; R.D. curve reproduced in Fig. 1. A sample for analysis was distilled at 250° and 0.08 mm.

Anal. Calcd. for $C_{29}H_{44}O$: C, 85.23; H, 10.85. Found: C, 84.11; H, 10.36.

For more adequate characterization, the **2,4-dinitrophenylhydrazone XXXb** was prepared in ethanol solution and

(79a) ADDED IN PROOF.—J. Jouanneteau and C. Mentzer, *Compt. rend.*, **246**, 2195 (1958), have reported the preparation of this substance as an oil.

(80) Compared to λ_{max} 294 mμ, log ε 1.52, for the parent ketone XXV measured in the same solvent pair.

purified by filtration (in benzene) through alumina and recrystallization from chloroform–ethanol; m.p. 257–260°, $\lambda_{max}^{CHCl_3}$ 410 mμ, log ε 4.58, $[\alpha]_{589}$ +140° (*c* 0.017 in dioxane).

Anal. Calcd. for $C_{35}H_{48}N_4O_4$: N, 9.52. Found: N, 9.77.

(b) **From 4α-Ethylcholestan-3-one (XXV).**—The tribromination[34] of 0.41 g. of the ketone XXV in 5 cc. of glacial acetic acid was conducted at 15° with 14.5 cc. of a bromine–acetic acid solution containing 34 mg./cc. of bromine. The ketone was originally in suspension but dissolved during the course of the bromine addition which required 20 min. After stirring for an additional 4 hr., the oily dibromo ketone XXIX (λ_{max}^{EtOH} 266 mμ) was isolated in the usual manner and dehydrobrominated directly with lithium carbonate and lithium bromide[36] exactly as described above. The oily trienone XXXa (0.38 g.) was again purified by chromatography on alumina, whereupon it exhibited λ_{max}^{EtOH} 225, 259 (inflect.) and 307 mμ, log ε 4.16, 3.92 and 4.14. Its infrared spectrum was identical with that of the trienone prepared according to (a) but, for further identification, a portion was transformed into the dark red 2,4-dinitrophenylhydrazone, m.p. 258–260°, alone or on admixture with the above described specimen; $\lambda_{max}^{CHCl_3}$ 412 mμ, log ε 4.59.

Anal. Calcd. for $C_{35}H_{48}N_4O_4$: C, 71.39; H, 8.22; N, 9.52. Found: C, 71.58; H, 8.32; N, 9.39.

When 4α-ethylcholestan-3-one (XXV) was dibrominated, the reaction proceeded in part by disproportionation as reported already for a similar 4α-methyl-3-keto-5α-steroid[34] since chromatography of the dehydrobromination product afforded two products; the initially eluted oil, λ_{max}^{EtOH} 293 mμ, log ε 4.03 appeared to be largely **4-ethyl-Δ^{4,6}-cholestadien-3-one** and formed a red 2,4-dinitrophenylhydrazone, m.p. 255–261° (from chloroform–ethyl acetate), $\lambda_{max}^{CHCl_3}$ 396 mμ, log ε 4.45.

Anal. Calcd. for $C_{35}H_{50}N_4O_4$: C, 71.15; H, 8.53; N, 9.48. Found: C, 71.51; H, 8.92; N, 9.33.

The material eluted later formed a 2,4-dinitrophenylhydrazone, m.p. 258–260°, $\lambda_{max}^{CHCl_3}$ 410 mμ, log ε 4.43, which proved to be identical with XXXb.

Monobromination of 19-Norandrostan-17β-ol-3-one Acetate (XXXIIIa).—19-Norandrostan-17β-ol-3-one 17-acetate (XXXIIIa)[81] (100 mg.) in 10 cc. of glacial acetic acid was treated with a solution of 52 mg. of bromine in 1.9 cc. of acetic acid. Isolation in the usual manner produced an oil (112 mg.) which could not be crystallized, even after chromatography on silica gel. Its structure as **2β-bromo-19-norandrostan-17β-ol-3-one acetate (XXXIIIb)** was established as follows: The spectroscopic evidence[39–41] compared with the corresponding properties of XXXIIIa[81] proves the axial nature of the halogen atom: $\lambda_{max}^{CHCl_3}$ 5.83 μ, λ_{max}^{EtOH} 312 mμ, log ε 1.56; R.D. (*c* 0.066) in methanol: $[\alpha]_{700}$ +15°, $[\alpha]_{589}$ +55°, $[\alpha]_{330}$ +710°, $[\alpha]_{290}$ −276°.

The location of the axial bromine atom at C-2 was confirmed by collidine dehydrobromination and conversion of the crude dehydrobromination product (λ_{max}^{EtOH} 229 mμ, log ε 3.98) directly into the orange-red **Δ^1-19-norandrosten-17β-ol-3-one acetate 2,4-dinitrophenylhydrazone**, which could also be obtained in one step by 2,4-dinitrophenylhydrazine–acetic acid treatment[32] of XXXIIIb, m.p. 246–249° (after recrystallization from chloroform–ethyl acetate), $\lambda_{max}^{CHCl_3}$ 381 mμ, log ε 4.34.

Anal. Calcd. for $C_{26}H_{32}N_4O_6$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.55; N, 10.99.

Reduction of the Ketone XVI. (a) With Lithium and Liquid Ammonia.—The reduction of 175 mg. of the ketone XVI in 15 cc. of dioxane was carried out with lithium–ammonia–methanol as described above for the reduction of XX to XXVIa. Recrystallization from hexane–benzene provided 145 mg. of colorless crystals (in two crops: 65 mg., m.p. 150–153° and 80 mg., m.p. 146–153°), while the analytical sample of the **alcohol XXXIa** formed wool-like clusters of colorless crystals, m.p. 151–153°, $[\alpha]_D$ −73°.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.54; H, 11.66; O, 5.79. Found: C, 82.69; H, 11.38; O, 5.98.

The acetate XXXIb, prepared in acetic anhydride–pyridine solution at room temperature, crystallized from methanol as beautiful plates, m.p. 101–103°, $[\alpha]_D$ −78°, $\lambda_{max}^{CS_2}$ 5.78 and 5.95 μ.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 79.49; H, 10.68; O, 10.29.

(b) **With Lithium Aluminum Hydride.**—The ketone XVI (250 mg.) was reduced with lithium aluminum hydride in dioxane solution exactly as reported above for XXV. One recrystallization of the crude reaction product furnished 65 mg. of the equatorial alcohol XXXIa, m.p. 150–153°, $[\alpha]_D$ −73°, identical with the above described specimen. Chromatography of the mother liquors on 20 g. of alumina and elution with benzene–ether (4:1) provided 13 mg. of solid, m.p. 90–96°, which could be sublimed at 90° and 0.001 mm. On the basis of the micro-oxidation experiments[31] (Table I), this is almost certainly the axial **alcohol XXXII**. Further development of the chromatogram with the same solvent pair afforded an intermediate fraction—apparently a mixture of XXXIa and XXXII—and this was followed by 110 mg. of the equatorial alcohol XXXIa, whose infrared spectrum was identical with that of a sample prepared according to (a).

Monobromination of Ketone XVI.—A 200-mg. sample of the ketone XVI in 10 cc. of acetic acid was treated with one drop of hydrogen bromide–acetic acid solution followed by the dropwise addition of 116 mg. of bromine in acetic acid over a period of 1 hr. The solution was then poured into ice-water and the **bromo ketone XXXIV** was isolated with ether; yield 210 mg., m.p. 117–121°. Recrystallization from chloroform–methanol led to the analytical sample, m.p. 127–127.5°, whose spectroscopic properties[39–41] (for comparison see parent ketone XVI) were only consistent with an equatorial orientation of the bromine atom: $\lambda_{max}^{CHCl_3}$ 5.73 μ, λ_{max}^{EtOH} 284 mμ, log ε 1.83; R.D. (*c* 0.10) in methanol: $[\alpha]_{700}$ −58°, $[\alpha]_{589}$ −78°, $[\alpha]_{305}$ −1505°, $[\alpha]_{280}$ +169°.

Anal. Calcd. for $C_{19}H_{29}BrO$: C, 64.58; H, 8.27; N, 4.53. Found: C, 64.84; H, 8.21; O, 4.71.

The location of the bromine atom at C-2 was proved by heating a solution of 90 mg. of the bromo ketone XXXIV in 5 cc. of dimethylformamide with constant stirring in an atmosphere of nitrogen with 160 mg. of lithium carbonate and 190 mg. of lithium bromide. After 15 hr. at 100°, the **Δ^1-3-ketone XXXVa** (61 mg. of semi-solid, λ_{max}^{EtOH} 231 mμ, log ε 3.82) was isolated with ether and was transformed directly into the **2,4-dinitrophenylhydrazone XXXVb**, m.p. 198–199° (from chloroform–ethanol), $\lambda_{max}^{CHCl_3}$ 381 mμ,[33] log ε 4.58.

Anal. Calcd. for $C_{25}H_{32}N_4O_4$: C, 66.35; H, 7.13; N, 12.38. Found: C, 66.19; H, 7.50; N, 12.21.

When the dehydrobromination was attempted with 2,4-dinitrophenylhydrazine in acetic acid solution in the usual manner,[32] over 70% of bromo ketone could be recovered.[82] A similar resistance toward dehydrobromination was noted when 32 mg. of the bromo ketone XXXIV was heated under reflux with 2 cc. of γ-collidine. No precipitate was formed during the first 75 min. and even after heating for 2 hr., only 7 mg. (38%) of collidine hydrobromide (water soluble) was isolated. The crude residue exhibited λ_{max}^{EtOH} 239 mμ, log ε 3.65, which indicated the presence of some of the Δ^1-ketone XXXVa contaminated by the Δ^4-isomer XXXVIa.

The origin of this contamination appears to be thermal rearrangement of the bromine atom to C-4 and spontaneous dehydrobromination. This could be supported by two experiments: (a) When 70 mg. of the bromo ketone was dissolved in 2 cc. of glacial acetic acid and the solution concentrated at 100° in a current of nitrogen, followed by dilution with water and extraction with ether, there was obtained 40 mg. of semi-solid with λ_{max}^{EtOH} 247 mμ, log ε 3.37. (b) Repeated recrystallization of the bromo ketone XXXIV afforded mother liquors, whose infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.78, 6.00, 6.20 μ) indicated the presence of some Δ^4-3-ke-

(81) Prepared by acetylation of 19-norandrostan-17β-ol-3-one (A. Bowers, H. J. Ringold and R. I. Dorfman, THIS JOURNAL, **79**, 4556 (1957)) and recrystallized from ether–hexane: m.p. 95–97°, $\lambda_{max}^{CHCl_3}$ 5.80 (shoulder), 5.83 and 7.95 μ, λ_{max}^{EtOH} 291 mμ (log ε 1.47); R.D. (*c* 0.15) in methanol: $[\alpha]_{700}$ +25°, $[\alpha]_{589}$ +27°, $[\alpha]_{305}$ +912°, $[\alpha]_{270}$ −1252°. *Anal.* Calcd. for $C_{26}H_{34}O_2$: C, 74.96; H, 10.06; O, 14.98. Found: C, 75.13; H, 9.65; O, 15.01.

(82) When the conditions[32] were modified by concentrating the acetic solution on the hot-plate in a current of nitrogen, adding more acetic acid and repeating this process three times, there was obtained a mixture of reddish rosettes and yellow prisms. A sufficient amount of the former could be separated manually under the microscope so that its ultraviolet absorption maximum could be determined: $\lambda_{max}^{CHCl_3}$ 382 mμ, indicating the formation of a small amount of XXXVb.

tone XXXVI. Indeed when 100 mg. of such oily mother liquor material was heated in acetic acid solution with 65 mg. of 2,4-dinitrophenylhydrazine, there was obtained a bright red precipitate which was collected and recrystallized from chloroform–ethanol affording 45 mg. of **2,4-dinitrophenylhydrazone XXXVIb**, m.p. 202–204°. The position of the double bond was indicated[33] by the absorption maximum, $\lambda_{max}^{CHCl_3}$ 397 mμ, log ε 4.46.

Anal. Calcd. for $C_{25}H_{32}N_4O_4$: C, 66.35; H, 7.13. Found: C, 66.40; H, 7.18.

Tribromination of Ketone XVI.—The ketone XVI (137 mg.) in 5 cc. of glacial acetic acid was treated at room temperature over a period of 10 min. with a solution of 240 mg. of bromine in 6.5 cc. of acetic acid. The yellow solution was stirred for 1 hr., diluted with water and the crude bromo ketone (λ_{max}^{EtOH} 265 mμ, log ε 3.95) was dehydrobrominated directly by heating for 24 hr. at 100° with 10 cc. of dimethylformamide, 230 mg. of lithium carbonate and 260 mg. of lithium bromide. Isolation of the dehydrobromination product (88 mg.) was carried out as described above for 4-ethyl-1,4,6-cholestatrien-3-one (XXXa) and purification was performed by chromatography on 10 g. of Alcoa F-20 alumina. Elution with benzene afforded 63 mg. of the **trienone XXXVIIa** as a yellowish oil. The substance resisted all attempts at crystallization and the ultraviolet extinction indicated that the substance was not completely pure. The presence of the 1,4,6-trienone chromophore, however, was established quite definitely by the rotatory dispersion curve (Fig. 1) and the characteristic triple ultraviolet absorption maxima: λ_{max}^{EtOH} 232, 256 and 302.5 mμ; log ε 3.89, 3.88 and 3.89. The analytical sample was distilled at 0.01 mm.

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01; O, 5.97. Found: C, 84.49; H, 9.61; O, 6.73.

For adequate characterization, a sample of the oily trienone XXXVIIa was transformed into its dark red **2,4-dinitrophenylhydrazone XXXVIIb**, which was purified by chromatography on acid-washed alumina (benzene elution) and successive recrystallization from chloroform–ethanol and chloroform–ethyl acetate; m.p. 216–218°, $\lambda_{max}^{CHCl_3}$ 410 mμ, log ε 4.38, $[\alpha]_{539}$ −275° (*c* 0.032 in methanol).

Anal. Calcd. for $C_{25}H_{28}N_4O_4$: C, 66.94; H, 6.29; N, 12.49. Found: C, 66.90; H, 6.70; N, 12.07.

Deuterium Incorporation in Epoxynorcafestadienone (II).[83]—A mixture of 100 mg. of epoxynorcafestadienone (II), 3 cc. of 95% deuterioethanol (containing 5% of deuterium oxide) and 0.5 cc. of a 20% solution of sodium deuteride in deuterium oxide was heated under reflux for 15 min. in an atmosphere of nitrogen and the solvents removed *in vacuo*. To the residue was added 3 cc. of 95% deuterioethanol and 0.5 cc. of deuterium oxide and the mixture was heated under reflux for 10 min. The solvents were again removed and the exchange treatment was repeated twice. After the last evaporation, 3 cc. of deuterium oxide was added (*p*H of solution above 11), the product was extracted with ether, dried over sodium sulfate and evaporated to dryness to afford 92 mg. of colorless solid which was sublimed at 140° and 0.25 mm. for analysis: found,[84] 8.32 absolute atom-% D, which corresponds to exactly 2.0 hydrogen atoms of II replaced by deuterium.

Epoxycafestadiene (LVII).—A mixture of 7.6 g. of the aldehyde VI,[13,14] 37 cc. of 85% hydrazine hydrate and 150 cc. of diethylene glycol was heated at 95° for 1 hr., 7.6 g. of potassium hydroxide was added and heating under reflux was continued for 1 hr. The condenser was removed, heating was continued until the internal temperature reached 195° and the mixture then was refluxed for 4 hr. Isolation of the product was performed in the usual manner by ether extraction followed by distillation at 120° and 0.01 mm., which yielded 4.2 g. of LVII, m.p. 67–69°. The analytical sample was prepared by repeated recrystallization from methanol and high vacuum sublimation, m.p. 69–70°, $[\alpha]_D$ −156°, no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.45; H, 9.92. Found: C, 84.05; H, 9.86.

Hydrogenolysis of Epoxycafestadiene (LVII).—A solution of 3.0 g. of LVII in 130 cc. of glacial acetic acid was shaken in an atmosphere of hydrogen with 1.28 g. of prereduced platinum oxide catalyst for 4 hr. (room temperature) and then at 50–60° for an additional 16 hr. The product then was worked up exactly as described above for the hydrogenolysis of epoxynorcafestadiene (X), including saponification with 1% methanolic potassium hydroxide (the formation of acetates was indicated by infrared bands at 5.80 and 8.0 μ) and chromatography. No work was done on the earlier eluates, which may correspond to hydrocarbon and tetrahydrofurans (see XI, XII), but the alcohol fraction was crystallized from methanol to yield 0.6 g. of the **alcohol LVIII**, m.p. 120–123°. Further recrystallization and sublimation *in vacuo* raised the m.p. to 124–126°, $[\alpha]_D$ −59°; the rotatory dispersion curve already has been reproduced.[49]

Anal. Calcd. for $C_{29}H_{34}O$: C, 82.69; H, 11.80. Found: C, 83.12; H, 11.53.

Oxidation of 140 mg. of the alcohol LVIII was performed exactly as described above for the lower homolog XIII and gave 120 mg. of oily ketone (LIX with equatorial (α)-ethyl group). This was transformed by passage in 1:1 hexane–benzene solution over basic alumina into 115 mg. of crystalline **ketone LIX**, m.p. 60–70°. One recrystallization from ethanol and sublimation *in vacuo* provided the analytical sample, m.p. 81–83°, $[\alpha]_D$ −89° (methanol), $\lambda_{max}^{CHCl_3}$ 5.84 μ, whose rotatory dispersion curve already has been published.[49] The ketone remained unchanged when heated with 2% methanolic potassium hydroxide solution for 1 hr., as demonstrated by determination of m.p., infrared spectrum and rotatory dispersion.

Anal. Calcd. for $C_{29}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.32; H, 11.19.

Its yellow **2,4-dinitrophenylhydrazone** was prepared in glacial acetic acid solution[32] and recrystallized from chloroform–methanol; m.p. 211–212°. Its ultraviolet absorption maximum, $\lambda_{max}^{CHCl_3}$ 368 mμ, log ε 4.20, was essentially identical with that ($\lambda_{max}^{CHCl_3}$ 369 mμ, log ε 4.24), of friedelin (XVIII) 2,4-dinitrophenylhydrazone (m.p. 295–296°).

Anal. Calcd. for $C_{26}H_{36}N_4O_4$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.63; H, 7.74; N, 11.78.

The ethylene thioketal LXI was prepared by adding 0.2 cc. of boron trifluoride etherate[85] to a solution of 165 mg. of the ketone LIX in 0.2 cc. of ethanedithiol. After a few minutes, crystals separated and addition of methanol completed precipitation. The solid (160 mg., m.p. 124–127°) was collected and recrystallized from methanol–acetone; m.p. 130–131°, $[\alpha]_D$ −67°, no infrared carbonyl absorption.

Anal. Calcd. for $C_{31}H_{50}S_2$: C, 72.49; H, 9.96. Found: C, 72.45; H, 10.09.

Desulfurization was accomplished by heating 160 mg. of the thioketal LXI with an excess of W-4 Raney nickel catalyst in 50 cc. of acetone under reflux for 20 hr. Filtration of the catalyst, evaporation of the acetone and trituration of the residue with methanol led to colorless crystals of the **hydrocarbon LXII**, which exhibited m.p. 63–64° (40 mg.) after recrystallization from methanol.

Anal. Calcd. for $C_{29}H_{54}$: C, 87.51; H, 12.49. Found: C, 87.49; H, 12.45.

Lithium Aluminum Hydride Reduction of Ketone LIX.—The reduction of 100 mg. of the ketone LIX in 10 cc. of dioxane was carried out with 100 mg. of lithium aluminum hydride for 45 min. at 95°. After addition of ethyl acetate and water, the **alcohol LX** was extracted with chloroform and recrystallized from hexane; m.p. 145–146°. The melting point was unchanged after sublimation and the oxidation rate is given in Table I.

Anal. Calcd. for $C_{29}H_{51}O$: C, 82.69; H, 11.80. Found: C, 82.52; H, 11.65.

DETROIT, MICH.

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(84) Deuterium analysis by J. Nemeth, University of Illinois.

(85) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).