region, where each isomer exhibited a unique ratio of intensities, and slight displacements, of three prominent absorption bands: I, 1030 > 1058 > 1007; II, 997 > 1030 > 990 (shoulder); III, 1023 > 1055 > 1008; IV, 1060 > 1035 > 1010.

EVANSTON, ILL.

[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A., AND THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

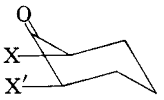
Optical Rotatory Dispersion Studies. XXIII.[1] α-Haloketones (Part 3)[2]

BY CARL DJERASSI, IRMA FORNAGUERA[3] AND O. MANCERA

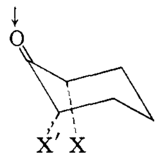
RECEIVED NOVEMBER 3, 1958

The earlier work on the optical rotatory dispersion of steroidal α-haloketones has been extended to include equatorial iodo- and fluoroketones. An examination of the rotatory dispersion curves of 21-fluoro-, chloro-, bromo- and iodo-20-keto steroids as well as of 17α-chloro- and 17α-bromo-20-ketones suggests that under certain circumstances, the "axial haloketone rule" may be employed to differentiate between free rotational isomers.

A systematic study[2] of the rotatory dispersion curves of a variety of α-bromo- and α-chloroketones of the steroid series has led to certain generalizations[2,4] which can be summarized briefly as follows: In a cyclohexanone (Ia) existing in the chair form,[5] introduction of *equatorial* chlorine or bromine in the α-(Ib) or α'-(Ic) positions does not affect the sign of the single Cotton effect curve[6] of the parent ketone Ia although there may be noted differences in amplitude.[6] On the other hand *axial* chlorine or bromine may alter the situation profoundly and the sign of the Cotton effect curve can be predicted by employing the following, empirical device.[2,4] By looking down the O=C axis as indicated by the arrow (II), a cyclohexanone derivative with chlorine or bromine to the left (IIa) of the observer will show a negative Cotton effect while if the halogen atom is located to the right (IIb), a positive Cotton effect will be predicted.



Ia, X = X' = H
b, X = Cl or Br; X' = H
c, X = H; X' = Cl or Br



IIa, X = Cl or Br; X' = H
b, X = H; X' = Cl or Br

This "axial haloketone rule"—for which no exception has as yet been noted—affords a simple means to establish absolute configurations and it has been used[7] recently to demonstrate conformational mobility in *trans*-2-chloro-5-methylcyclohexanone. In order to define more precisely the scope of these generalizations, we have determined the optical rotatory dispersion curves of a number of additional steroidal α-haloketones and the present paper is concerned with these results.

In our earlier communication,[2] attention was directed to the observation that the few steroidal α-fluoroketones which had been measured—9α-fluoro-11-ketones or 12α-fluoro-11-ketones—did not follow this rule since in these cases the axial fluorine had exactly the opposite effect from that observed for chlorine or bromine; no data were available for α-iodoketones.

We have now repeated the preparation of 2α-iodocholestan-3-one (IIIa)[8] and measured its rotatory dispersion curve. This substance was of particular interest since its ultraviolet absorption maximum occurs at 258 mμ[8] as compared to 279–282 mμ recorded[9] for 2α-chloro- (IIIc) and 2α-bromocholestan-3-one (IIIb). In view of the excellent correlation between ultraviolet absorption and rotatory dispersion data,[2] it might have been anticipated that the peak (or trough) of 2α-iodocholestanone (IIIa) would be encountered at a lower wave length than reported[2] for the chloro and bromo analogs, but this did not prove to be the case. As can be seen from the data listed in the Experimental section, 2α-iodocholestan-3-one exhibited a positive Cotton effect curve with a peak in the 310 mμ region, identical with that observed[2] for 2α-chloro- or 2α-bromocholestan-3-one. The simplest explanation is that in addition to the reported[8] ultraviolet absorption maximum at 258 mμ, there exists a carbonyl band in the 280 mμ region (apparently masked by the stronger 258 mμ maximum and hence not detected) which is optically active and which is responsible for the observed rotatory dispersion curve.

Quite recently, 2α-fluorocholestan-3-one (IIId)—the first known steroidal equatorial α-fluoroketone—has been synthesized[10] and its rotatory dispersion curve also has been found to be characterized by a single, positive Cotton effect. From the data collected in Table I, one can enlarge the scope of our earlier generalization[2] by stating that *equatorial* halogen does not appear to alter the sign of the Cotton effect of the parent ketone, irrespective of

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[1] Paper XXII, C. Djerassi, L. A. Mitscher and B. J. Mitscher, THIS JOURNAL, **81**, 947 (1959).

[2] Part 2, C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

[3] This material represents part of the professional thesis submitted by Srta. Irma Fornaguera to the Escuela Nacional de Ciencias Químicas de la Universidad Nacional Autónoma de México for the degree "Químico Farmacéutico Biólogo."

[4] C. Djerassi and W. Klyne, THIS JOURNAL, **79**, 1506 (1957).

[5] The applicability of these generalizations to boat forms will be discussed in a forthcoming article from this Laboratory.

[6] For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

[7] C. Djerassi and L. E. Geller, *Tetrahedron*, **3**, 319 (1958).

[8] G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

[9] R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

[10] R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958). We are greatly indebted to these investigators for a gift of 2α-fluorocholestan-3-one (IIId).

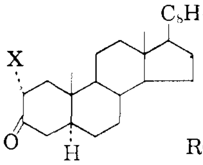
the nature of the halogen atom, nor is the amplitude or position of the peak affected to any marked extent. For axial substituents, the earlier rule[2] still applies so far only to chlorine or bromine.

Prior to the above measurements, we had synthesized a homologous series[11] of 21-halo-20-keto steroids (IVa–d) encompassing all four halogen atoms in order to examine the effect of different halogen atoms upon the rotatory dispersion of an acyclic ketone. The preparation of these haloketones was unexceptional: 21-bromoallopregnan-3β-ol-20-one acetate (IVb) and the corresponding 21-chloro derivative IVc were obtained by treating Δ^{20}-allopregnene-3β,20-diol diacetate (V)[12] with either N-bromosuccinimide or N-chlorosuccinimide. A sample of 21-iodoallopregnan-3β-ol-20-one (IVa) was available in this Laboratory and 21-fluoroallopregnan-3β-ol-20-one (IVd) was synthesized by warming IVa with silver fluoride in acetonitrile.[13] As shown in Table II, all four ketones (IVa–d) exhibited positive Cotton effect curves, the molecular amplitudes being of the same order of magnitude when compared with that of the halogen-free allopregnan-3β-ol-20-one (IVe).[14] In contrast to the cyclic ketones (Table I), in this series the position of the peak progressively shifts toward the visible in going from fluorine to iodine (Table II). Here again, there exists no correlation between the position of the rotatory dispersion peak and the observed ultraviolet absorption maximum of the 21-iodoketone IVa and it is conceivable—as suggested above with 2-iodocholestan-3-one (IIIa)—that there is present a second (optically active) absorption band around 300-310 mμ due to the carbonyl group which could not be detected in an ordinary spectrophotometer. Dispersion measurements also have been taken in non-polar solvents (see Experimental) and the expected[15] bathochromic shift was noted.

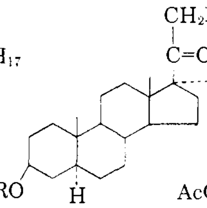
In connection with the above work it appeared of interest to examine the effect of a halogen atom in the alternate location (C-17) of a 20-keto steroid. In such a case, a 17α-halogen atom is in a *quasi*-axial position and thus might exert a more noticeable influence. Indeed, rotatory dispersion measurements of 17α-bromoallopregnan-3β-ol-20-one acetate (VI) and of 5α,6β,17α-trichloropregnan-3β-ol-20-one 3-acetate (VII)—their syntheses being described in the Experimental section—revealed a striking feature in that both ketones exhibited a negative Cotton effect curve. Two reasons could be offered to explain this unusual result:

(a) Halogenation of the Δ^{17}-enol acetate actually leads to the 17β-halo-17α-acetyl steroid (VIII). Such a structure would be expected to give a negative Cotton effect curve as has already been noted[16] for the halogen-free 17-iso-(α)-20-ketone VIII (X = H). However, such an explanation seems unsatisfactory since it would require halogenation of the Δ^{17}-enol from the β- rather than expected[17] α-side. Conclusive proof for the formation of 17α-bromo-20-ketones in the bromination of 20-ketones has been presented very recently[18] and consequently a structure such as VIII is untenable as an explanation for the observed negative Cotton effect.

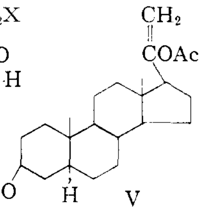
(b) A much more attractive rationalization, consistent with all experimental facts, can be presented by assuming that the "axial haloketone rule"[4] is also operative in acetylcycloalkanes (most likely also in acylcycloalkanes) with the halogen atom attached to the ring carbon.[19] When this halogen atom is present in an axial or *quasi*-axial orientation, then the "axial haloketone rule" can be applied and this approach appears to offer a means of distinguishing between "free-rotational" isomers. For instance, in a 17α-bromo-20-keto steroid (VI), the acetyl side chain is subject to free rotation although the other surrounding substituents—in particular the angular methyl group at C-13—will obviously restrict the various possible spatial situations. If one examines a model of rings C and D of VI by looking along the 13–17 bond from the C-18 angular methyl group, then the two most favored rotational isomers (IX and X) are those in which the two substit-



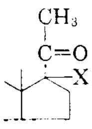
IIIa, X = I
b, X = Br
c, X = Cl
d, X = F
e, X = H



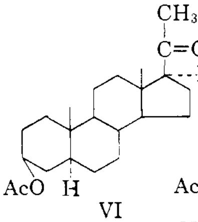
IVa, R = H; X = I
b, R = Ac; X = Br
c, R = Ac; X = Cl
d, R = H; X = F
e, R = X = H



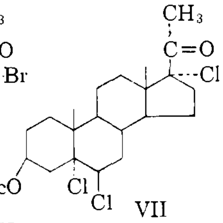
V



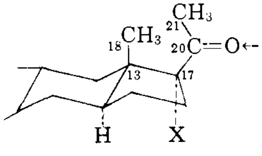
VIII



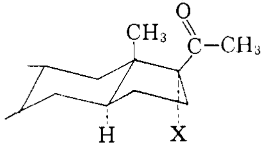
VI



VII



IX



X

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(11) These compounds differ only in the nature of the 3β-substituents, which are represented by either hydroxyl or acetoxyl. As reported in an earlier paper (C. Djerassi and W. Closson, THIS JOURNAL, **78**, 3761 (1956)) such structural changes play only a negligible role in the anomalous portion of the rotatory dispersion curve.

(12) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *ibid.*, **74**, 2810 (1952).

(13) P. Tannhauser, R. J. Pratt and E. V. Jensen, *ibid.*, **78**, 2658 (1956); B. Helferich and R. Gootz, *Ber.*, **62**, 2505 (1929).

(14) C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(15) C. Djerassi, R. Riniker and B. Riniker, THIS JOURNAL, **78**, 6377 (1956).

(16) C. Djerassi, *Bull. soc. chim. France*, 741 (1957).

(17) T. F. Gallagher and T. H. Kritchevsky, THIS JOURNAL, **72**, 882 (1950).

(18) N. L. Wendler, R. P. Graber and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

(19) Translated into steroid terms, this would apply to a 17-bromo (or chloro)-20-ketone.

TABLE I

MOLECULAR ROTATORY DISPERSION PEAKS OF 2-HALOCHOLESTANONES

Substance	Peak, mμ	Mol. rot.[a] (MeOH)	$\lambda_{\text{MeOH}}^{\max}$, m$\mu$
Cholestan-3-one (IIIe)	307[b]	+3711°	286[d]
2α-Fluorocholestan-3-one (IIId)	309	+2653	280
2α-Chlorocholestan-3-one (IIIc)	310[c]	+3136	279[d]
2α-Bromocholestan-3-one (IIIb)	310[c]	+3187	282[d]
2α-Iodocholestan-3-one (IIIa)	315	+4401	258

[a] Molecular rotation = specific rotation × mol. wt./100. [b] See C. Djerassi, W. Closson and A. E. Lippman, THIS JOURNAL, **78**, 3163 (1956). [c] See ref. 2. [d] In ethanol (ref. 9); the substance is too insoluble in methanol for satisfactory ultraviolet measurement.

TABLE II

MOLECULAR ROTATORY DISPERSION PEAKS OF 21-HALO-20-KETO STEROIDS

Substance	Peak, mμ	λMol.rot.[a] (MeOH sol.)	$\lambda_{\max}^{\text{MeOH}}$, m$\mu$
Allopregnan-3β-ol-20-one (IVe)	307.5[b]	+8881°	286
21-Fluoroallopregnan-3β-ol-20-one (IVd)	307.5	+7923[c]	284
21-Chloroallopregnan-3β-ol-20-one 3-acetate (IVc)	312.5	+6735	282
21-Bromoallopregnan-3β-ol-20-one 3-acetate (IVb)	327.5	+6524	292–294
21-Iodoallopregnan-3β-ol-20-one (IVa)	340	+8316	268–270

[a] Molecular rotation = specific rotation × mol. wt./100 [b] See ref. 14. [c] Independent measurement on another instrument showed $[M]_{307.5}$ +7380°.

uents attached to C-20, namely, the carbonyl oxygen and the C-21 methyl group, are approximately to the right and left of the C-18 angular methyl group.[20] Applying now the "axial haloketone rule"[4] (see arrows in IX and X), it will be seen that a negative Cotton effect will be predicted for rotational isomer IX and a positive Cotton effect for isomer X. *It would appear, therefore, that under certain circumstances, the optical rotatory dispersion curve can offer decisive information on the preferred position of a rotational isomer (in this case isomer IX*[20a]*).*

Experimental[21,22]

21-Bromo-allopregnan-3β-ol-20-one Acetate (IVb).—A mixture of 1.0 g. of Δ^{20}-allopregnene-3β,20-diol diacetate (V)[12] and 0.575 g. of N-bromosuccinimide in 10 cc. of anhydrous dioxane[23] was heated for 45 min. at 85° and then poured into ice-water. The product was isolated by extraction with methylene dichloride and after crystallization from methanol provided 0.78 g. of brownish crystals, m.p. 120–124°. Recrystallization from hexane–acetone yielded 0.545 g. of the colorless bromo ketone IVb, m.p. 142–143°; $\lambda_{\max}^{\text{MeOH}}$ 292–294 mμ, log ϵ 1.95; $\lambda_{\max}^{\text{hexane}}$ 306–308 mμ, log ϵ 2.01; R.D. (c 0.081) in methanol: $[\alpha]_{700}$ +30°, $[\alpha]_{559}$ +59°, $[\alpha]_{327.5}$ +1486°, $[\alpha]_{270}$ −2175°, $[\alpha]_{267.5}$ −2112°; R. D. (c 0.091) in octane: $[\alpha]_{700}$ +40°, $[\alpha]_{589}$ +88°, $[\alpha]_{337.5}$ +1947°, $[\alpha]_{280}$ −2683°, $[\alpha]_{262.5}$ −2400°; R.D. (c 0.062) in hexane: $[\alpha]_{700}$ +55°, $[\alpha]_{589}$ +73°, $[\alpha]_{335}$ +1863°, $[\alpha]_{300}$ −752°.

Anal. Calcd. for $C_{23}H_{35}BrO_3$: C, 62.87; H, 8.03; Br, 18.19; O, 10.92. Found: C, 62.91; H, 8.09; Br, 18.82; O, 11.10.

21-Chloro-allopregnan-3β-ol-20-one Acetate (IVc).—The reaction of 1.0 g. of the enol acetate V and 0.358 g. of N-chlorosuccinimide[23] was carried out exactly as described in the preceding experiment. The oily product was chromatographed on 30 g. of silica gel, eluted with benzene and recrystallized from methanol; yield 0.23 g., m.p. 114–115°, $\lambda_{\max}^{\text{MeOH}}$ 282 mμ, log ϵ 1.84; $\lambda_{\max}^{\text{hexane}}$ 294–298 mμ, log ϵ 1.81; R.D. (c 0.073) in methanol: $[\alpha]_{700}$ +29°, $[\alpha]_{589}$ +56°, $[\alpha]_{312.5}$ +1705°, $[\alpha]_{262.5}$ −2585°; R.D. (c 0.10) in octane: $[\alpha]_{700}$ +43°, $[\alpha]_{589}$ +71°, $[\alpha]_{322.5}$ +1846°, $[\alpha]_{280}$ −2210°; R. D. (c 0.061) in hexane: $[\alpha]_{700}$ +33°, $[\alpha]_{559}$ +86°, $[\alpha]_{320}$ +1940°, $[\alpha]_{300}$ +55°.

Anal. Calcd. for $C_{23}H_{35}ClO_3$: Cl, 8.97; O, 12.15. Found: Cl, 8.34; O, 12.02.

21-Iodo-allopregnan-3β-ol-20-one (IVa).—A sample of the iodoketone[24] was recrystallized from methanol and then from ether, whereupon it exhibited m.p. 138–139° dec.; $\lambda_{\max}^{\text{MeOH}}$ 268–270 mμ, log ϵ 2.62; $\lambda_{\max}^{\text{hexane}}$ 274–276 mμ, log ϵ 2.61[25]; R.D. (c 0.097) in methanol: $[\alpha]_{700}$ +87°, $[\alpha]_{589}$ +119°, $[\alpha]_{340}$ +1873°, $[\alpha]_{292.5}$ −2336°; R.D. (c 0.097) in octane: $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +107°, $[\alpha]_{347.5}$ +2231°, $[\alpha]_{297.5}$ −2921°.

Anal. Calcd. for $C_{21}H_{33}IO_2$: C, 56.75; H, 7.48; I, 28.56; O, 7.20. Found: C, 56.44; H, 7.53; I, 28.21; O, 7.30.

21-Fluoro-allopregnan-3β-ol-20-one (IVd).—To 1.0 g. of the iodoketone IVa in 40 cc. of acetonitrile was added a suspension of 0.5 g. of silver fluoride in 2 cc. of water and 6 cc. of acetonitrile and, after heating with stirring for 6 hr. at 30–40°, the precipitate was filtered and most of the acetonitrile was removed by distillation under reduced pressure. The residue was poured into ice-water, the product was extracted with methylene dichloride and purified by chromatography on 25 g. of silica gel. The material eluted with benzene–ether mixtures (8:2, 7:3 and 6:4) was recrystallized from hexane–acetone to give 0.26 g. of the fluoroketone IVd, m.p. 150–153°. The analytical sample was obtained from ether, m.p. 157–159°; $\lambda_{\max}^{\text{MeOH}}$ 284 mμ, log ϵ 1.88; R.D. (c 0.041) in methanol: $[\alpha]_{700}$ + 44°, $[\alpha]_{589}$ +83°, $[\alpha]_{307.5}$ +2351°, $[\alpha]_{270}$ −2500°; R.D. (c 0.062) in hexane: $[\alpha]_{700}$ +58°, $[\alpha]_{589}$ +84°, $[\alpha]_{315}$ +1835°, $[\alpha]_{300}$ +826°.

Anal. Calcd. for $C_{21}H_{33}FO_2$: C, 74.96; H, 9.88; F, 5.64. Found: C, 74.47; H, 9.66; F, 4.97.

17α-Bromo-allopregnan-3β-ol-20-one Acetate (VI).—The bromination of 1.0 g. of Δ^{17}-allopregnene-3β,20-diol diacetate[26] with 0.575 g. of N-bromosuccinimide was performed exactly as described above for the isomeric Δ^{20}-enol acetate V and furnished 0.73 g. of the 17-bromo-20-ketone VI, m.p. 118–120° upon direct crystallization from methanol. Complete decolorization was achieved by treatment with Norit and repeated recrystallization from methanol, whereupon the analytical sample was obtained, m.p. 127–129°; $\lambda_{\max}^{\text{MeOH}}$ 296–298 mμ (log ϵ 2.04); R.D. (c 0.060) in methanol: $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ −30°, $[\alpha]_{315}$ −1340°, $[\alpha]_{300}$ −647°; R.D. (c 0.066) in hexane: $[\alpha]_{700}$ −30°, $[\alpha]_{559}$ −64°, $[\alpha]_{320}$ −1115°, $[\alpha]_{300}$ +153°.

Anal. Calcd. for $C_{23}H_{35}BrO_3$: C, 62.87; H, 8.03; Br, 18.19; O, 10.92. Found: C, 62.42; H, 8.24; Br, 18.56; O, 11.00.

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(20) In either case, the COCBr or COCCl angle will be about 105° (see ref. 9).

(20a) NOTE ADDED IN PROOF.—It has just been called to our attention that a similar conformation has also been proposed by W. Klyne ("Ciba Foundation Colloquia on Endocrinology," Little, Brown and Co., Boston, 1953, Vol. VII, p. 131) to explain the stereochemical course of certain chemical reductions of 20-keto steroids.

(21) The optical rotatory dispersion measurements were carried out in part by Mrs. T. Nakano (Wayne State University) and in part by Srta. Ana Luisa Pereda (Syntex, S.A.) according to the procedures outlined in ref. 15 except that the spectropolarimeter was equipped with a mechanically oscillating polarizer (H. Rudolph, *Proc. Instrum. Soc. Amer.*, Sept., 1956 (paper No. 56-3-1)).

(22) Melting points are uncorrected. The ultraviolet absorption measurements were performed by Dr. L. Throop and staff while the microanalyses are due to Dr. A. Bernhardt, Mülheim, Germany.

(23) Patterned after the synthesis of 21-iodo-20-ketones from enol acetates and N-iodosuccinimide (C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953)).

(24) This material was prepared some time ago in our laboratory by the general procedure of H. Ruschig, *Ber.*, **88**, 878 (1955).

(25) Measurements in a Cary recording ultraviolet spectrophotometer up to 350 mμ did not show any additional absorption maximum.

(26) C. W. Marshall, T. H. Kritchevsky, S. Lieberman and T. F. Gallagher, THIS JOURNAL, **70**, 1837 (1948).

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] $\lambda_{\max}^{\text{MeOH}}$ 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°, $[\alpha]_{320}$ +904°, $[\alpha]_{280}$ −676°, $[\alpha]_{270}$ −664°.

2α-Iodocholestan-3-one (IIIa),[8] $\lambda_{\max}^{\text{MeOH}}$ 256–258 mμ (log ε 2.86),[25] $\lambda_{\max}^{\text{hexane}}$ 260–262 mμ (log ε 2.82); R.D. (c 0.061) in methanol: $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +59°, $[\alpha]_{315}$ +858°, $[\alpha]_{290}$ −349°.

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DETROIT, MICHIGAN

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[27] The preparation of this substance by J. S. Mills and O. Candiani will be reported in another connection.

[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

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

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[4] U. S. Public Health Service predoctorate research fellow, 1956–1958.

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

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