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ON THE ABSOLUTE CONGIFURATION OF THE DITERPENE ALKALOIDS RELATED TO VEATCHINE AND ATISINE[1]

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The recent articles by Pelletier[2,3] on the relative stereochemistry of the diterpene alkaloids of the veatchine - atisine class[4] prompt us to record some of our own results in this field. As will be shown below, our investigations establish the absolute configuration of the C/D ring juncture and by inference, the complete absolute configuration of this group of alkaloids.

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[1] Alkaloid Studies XXVIII, S. C. Pakrashi, S. K. Roy, L. F. Johnson, T. George and C. Djerassi, <u>Chemistry & Industry</u> in press.

[2] S. W. Pelletier, J.Amer.Chem.Soc. 82, 2398 (1960).

[3] A. J. Solo and S. W. Pelletier, Chemistry & Industry 1108 (1960).

[4] For summary see K. Wiesner and Z. Valenta in L. Zechmeister's Progress in the Chemistry of Organic Natural Products. Springer Verlag, Vienna, 1958, Vol. XVI, pp. 26-89.

Garryfoline (I)[5,6] was transformed into cuauchichicine[5] hydrochloride acetate (m.p. 265° dec., $[\alpha]_D$ -55°) and then subjected to internal Hofmann elimination[7] to afford the azomethine II, which had been obtained earlier[4,5] in much poorer yield by selenium pyrolysis of veatchine or cuauchichicine. Treatment with nitrous acid in the presence of sodium acetate[8] led in nearly quantitative yield to the hemiacetal III (m.p. 203-205°, $\lambda_{max}^{chlf.}$ 5.79 μ, $[\alpha]_D$ -128°, negative R.D. Cotton effect[9] with trough at $[\alpha]_{322.5}$ -1494° (dioxane)), which was reduced by the Wolff-Kishner procedure to the alcohol IV (m.p. 89-90°, $[\alpha]_D$ -47°). The location of the primary hydroxyl group

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[5] C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, J. Amer. Chem. Soc. 77 4801, 6633 (1955).

[6] We are using a number system which we have proposed earlier for cafestol (C. Djerassi, M. Cais and L. A. Mitcher, J. Amer. Chem. Soc. 81, 2386 (1959)) and which has now been accepted also by Prof. L. H. Briggs for other diterpenoids of the phyllocladene group (see also ref. 13).

[7] Utilizing the conditions of D. Dvornik and O. E. Edwards, Can. J. Chem. 35, 860 (1957) in the atisine series.

[8] We are grateful to Dr. O. E. Edwards for providing us with the experimental details of a similar deamination conducted in the atisine series (O. E. Edwards and R. Howe, Proc. Chem. Soc. 62 (1959)).

[9] C. Djerassi, Optical Rotatory Dispersion: Applications to Organic Chemistry, Mc-Graw-Hill Book Co., New York 1960.

(at C-20 rather than C-19) and hence the structure of the hemiacetal III[10] was deduced from the extremely hindered nature of its corresponding aldehyde VI (vide infra) and the oxidation to the carboxylic acid V (m.p. 213-215°, $[\alpha]_D$ -40°). Through the cooperation of Dr. W. Simon,[11] the apparent dissociation constant of V was determined and found to be pK^*_{MCS} 9.49 as compared with pK^*_{MCS} 8.45 for deoxypodocarpic acid and pK^*_{MCS} 7.92 for dehydroabietic acid measured under the same conditions. This clearly eliminated C-4 as the point of attachment of the carboxyl group and the observed value of 9.49 is in reasonable agreement with the minimum value of 8.91 calculated by Simon's method[11] for V. The hindered nature of the primary hydroxyl group of IV is also evidenced by the observation that the alcohol could be eluted from neutral alumina (activity II) with hexane-benzene (1:1), while benzene-ether was required for the hemiacetal III.

Chromium trioxide - pyridine oxidation of IV furnished the aldehyde VI. Attempts to purify the crude aldehyde (m.p. 75-84°) by recrystallization or sublimation resulted in gradual conversion to the acid V. The extreme degree of steric hindrance imposed upon the aldehyde could be demonstrated by the

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[10] Structure III implies that the deamination proceeds through the double bond isomer of the azomethine II with which it is in equilibrium (see ref. 4).

[11] P. F. Sommer, V. P. Arya and W. Simon, Tetrahedron Letters No. 20, 18 (1960).

fact that its negative R.D. Cotton effect (trough at $[\alpha]_{320}$ -818° in methanol) was unaffected in the presence of hydrochloric acid, showing[9] that no acetal was produced, and that Wolff-Kishner reduction required extremely drastic conditions (3 days at 217°) to afford the hydrocarbon VII (m.p. 52°, $[\alpha]_D$ -43°), over 50% of the aldehyde VI being recovered after such treatment.

The hydrocarbon VII was not identical with either α- or β-dihydrophyllocladene, the C-16 isomeric hydrocarbons obtained by hydrogenation[12] of phyllocladene (VIII). As the relative and absolute configuration of phyllocladene (VIII) has been established,[13] garryfoline (I) and its relatives cannot possess the absolute configuration implicit in stereoformula VIII. Nevertheless, the nor-ketones IX and X derived[12,14] from phyllocladene (VIII) proved to be of importance in settling the absolute configuration of the C/D ring fusion of the diterpenoid alkaloids.

The negative rotatory dispersion Cotton effects of the ketones II and III obtained from garryfoline (I) are similar

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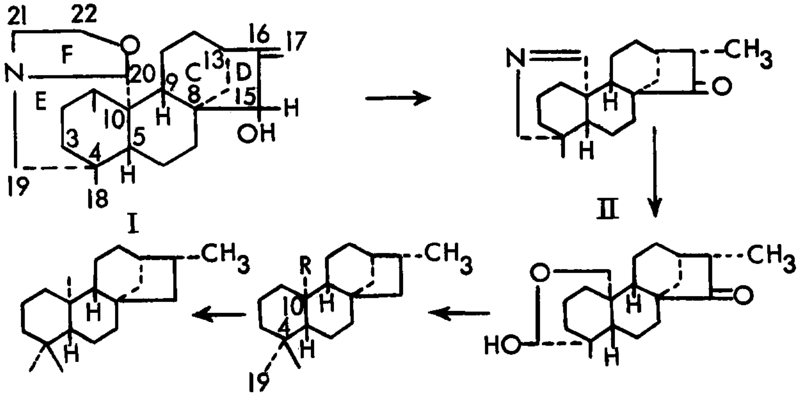
[12] C. W. Brandt, <u>New Zealand J. Sci. Techn.</u> **20**, 8B (1938).

[13] L. H. Briggs, B. F. Cain and R. C. Cambie, <u>Tetrahedron Letters</u> No. 8, 17 (1959); P. K. Grant and R. Hodges, <u>Tetrahedron</u> **8**, 261 (1960).

[14] R. Henderson and R. Hodges, <u>Tetrahedron</u> **11**, 226 (1960), as well as unpublished experiments by L. H. Briggs and collaborators.



I

II

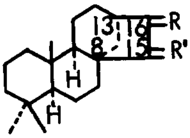
VII

IV R = CH_2OH

V R = CO_2H

VI R = CHO

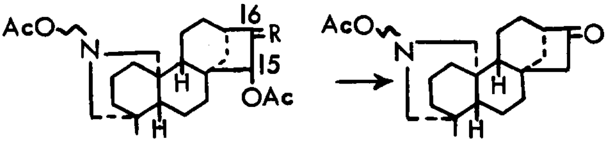
III



VIII R = CH_2; R' = H_2

IX R = O; R' = H_2

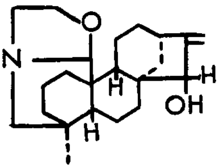
X R = H_2; R' = O



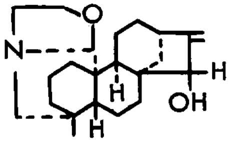
XI R = CH_2

XII R = O

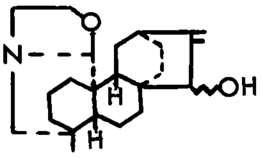
XIII



XIV



XV



XVI

to those observed for the 15-ketone X and other 15-ketones of the phyllocladene series. This suggests that the absolute configuration of the ring junctures at C-8 and C-13 of garryfoline (I) and phyllocladene (VIII) are identical. Further support for this supposition could be provided by oxidizing F-dihydrogarryfoline[5] diacetate (XI) (m.p. 105-106°, $[\alpha]_D$ -83°) in acetic acid solution with the osmium tetroxide-periodate reagent[15], the resulting 16-keto acetate XII (m.p. 146-147°, $[\alpha]_D$ -82°) exhibiting a positive Cotton effect (peak at $[\alpha]_{327.5}$ + 687° in dioxane solution) as does[16] the 16-ketone IX from phyllocladene. Most importantly, removal of the C-15 acetoxy group of XII with calcium in liquid ammonia provided the 16-ketone XIII (m.p. 69-70°, $[\alpha]_D$ -48°), whose positive Cotton effect was now practically superimposable upon that[16] of the phyllocladene 16-ketone IX. Since the configuration at C-9 will have no effect upon the sign of the Cotton effect, the governing factor[17] being the configuration at the ring junctions (C-8 and C-13) of the cyclopentanone ring, we can conclude safely that garryfoline (I) and phyllocladene (VIII) possess identical absolute configurations at these centers.

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[15] R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, J. Org. Chem. 21, 478 (1956).

[16] C. Djerassi, R. Riniker and B. Riniker, J. Amer. Chem. Soc. 78, 6362 (1956).

[17] See J. F. Grove, J. MacMillan, T. P. C. Mulholland and W. B. Turner, J. Chem. Soc. 3049 (1960),

Furthermore, as the hydrocarbon VII has been shown to be different from the dihydrophyllocladenes, the absolute configuration of garryfoline can only be represented by I, XIV or XV. If the latter were correct, then the aldehyde VI would not be expected to exhibit the extreme degree of hindrance mentioned above, as ring B would then exist in the boat form and would thus unshield the angular aldehyde on one side. Taken in conjunction with other arguments summarized by Solo and Pelletier,[3] only absolute configuration I for garryfoline is consistent with all the experimental facts. On this basis, our hydrocarbon VII should be the antipode of one of the possible reduction products of mirene (a stereoisomer of phyllocladene (VIII)), since the latter has been attributed[18] the same relative (but opposite absolute) stereochemistry at positions 5, 8, 9, 10 and 13, as shown for VII.

Garryfoline (I) has been interrelated[4,5] with veatchine (C-15 epimer of I) and garryine. Furthermore, an experimental connection has been achieved[2] with veatchine and atisine, so that the absolute configuration XVI can now be assigned to the latter. It is pertinent to note that Dvornik and Edwards[19] have proposed earlier the possibility that the A/B

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[18] L. H. Briggs, B. F. Cain, R. C. Cambie and B. K. Davis, Tetrahedron Letters No. 24, 18 (1960).

[19] D. Dvornik and O. E. Edwards, Chemistry & Industry 623 (1958).

ring juncture in atisine (XVI) may be antipodal to that of the steroids by molecular rotation difference calculations utilizing a degradation product in which ring C became phenolic. Furthermore, it is of considerable biogenetic significance that the present absolute configurational assignments coincide with those made by x-ray analysis[20] for some of the poly-oxygenated aconite alkaloids.

All rotations were determined in chloroform solution and satisfactory elementary analyses have been secured for all substances. We are indebted to the National Heart Institute of the National Institutes of Health for financial help (grant No. H-5048) and to Professor L. H. Briggs of the University of Auckland for providing us with several specimens for comparison purposes.

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[20] M. Przybylska and L. Marion, Can. J. Chem. 37, 1843 (1959). See also F. W. Bachelor, R. F. C. Brown and G. Büchi, Tetrahedron Letters No. 10, 1 (1960).