überein, wie der $\Delta[\Phi]$-Wert von + 123° für die 11-ständige Hydroxylgruppe[14].

3,11-Diketo-4-ätiensäuremethylester (XI)[11] erhält man durch mikrobiologische Hydroxylierung von Verbindung I mit *Rhizopus nigricans* E., wobei zunächst 11α-Hydroxy-3-keto-4-ätiensäuremethylester (XVIII)[15] entsteht, der anschliessend mit Chrom-VI-oxid in N,N-Dimethylformamid/Schwefelsäure[16] oxydiert wird.

Verbindung XI ist andererseits auch aus Cortisonacetat zugänglich: 21,21-Bismethoxy-4-pregnen-3,11,20-trion[17], durch MATTOX-Umlagerung[17] von Cortisonacetat erhältlich, wird in Anlehnung an die Methode von RE[18] in 11-Dehydro-corticosteron umgewandelt. Dessen oxydativer Abbau mit Chrom-VI-oxid in wässriger Essigsäure führt zur 3,11-Diketo-4-ätiensäure[11], die nach Veresterung mit Diazomethan schliesslich XI ergibt.

Die Tabelle gibt einen Überblick über Schmelzpunkte und optische Drehwerte[19] der dargestellten Verbindungen. Von allen angeführten Substanzen wurden Elementaranalysen, UV- und IR-Spektren angefertigt, die mit den angegebenen Strukturen in Einklang stehen[20].

Summary. Starting from methyl 3-oxo-4-etienate, the authors prepared 17β-hydroxymethyl-4-androsten-3-one and 11β-hydroxy-17β-hydroxymethyl-4-androsten-3-one. Chlorination of 17β-acetoxymethyl-4-androsten-3-one yielded 4-chloro-17β-acetoxymethyl-4-androsten-3-one. 17β-Hydroxymethyl-1,4-androstadien-3-one was obtained from 17β-hydroxymethyl-4-androsten-3-one, both by chemical and biological methods.

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Wissenschaftliche Laboratorien des VEB Jenapharm, Jena (DDR), 13. Mai 1965.

[14] Der Mittelwert aus den molaren Drehwertbeiträgen der 11β-Hydroxygruppe in Corticosteron, Hydrocortison, 11β-Hydroxyprogesteron und 11β-Hydroxytestosteron beträgt + 161°.

[15] F. REBER, A. LARDON und T. REICHSTEIN, Helv. chim. Acta *37*, 45 (1954).

[16] Zur Methode vgl. G. SNATZKE, Ber. dtsch. chem. Ges. *94*, 729 (1961).

[17] V. R. MATTOX, J. Am. chem. Soc. *74*, 4340 (1952).

[18] L. RE, Steroids *2*, 465 (1963).

[19] Schmelzpunkte sind unkorrigiert; optische Drehwerte in Chloroform, soweit nicht anders angegeben.

[20] Fräulein G. KRETZSCHMANN wird an dieser Stelle für ihre experimentelle Mitarbeit gedankt. Herrn Dr. K. HELLER verdanken wir Aufnahme und Interpretation der IR-Spektren.

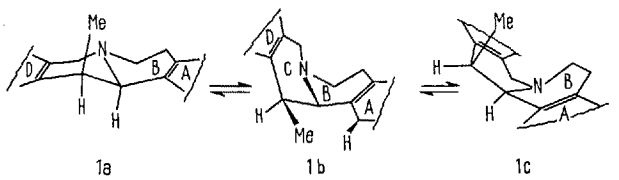
Stereochemistry of Corydaline and Related Alkaloids[1]

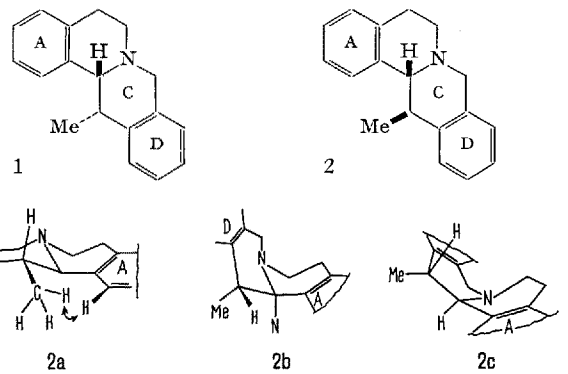
Conflicting reports exist on the stereochemistry of the protoberberine alkaloid corydaline. BERSCH[2] has suggested a *cis*-C(13), C(14) configuration for the alkaloid, whereas in a more recent proposal KONDO[3] has assigned the alternative *trans* stereochemistry at these positions.

A re-evaluation of the evidence is presented which supports the earlier assignment made by BERSCH[4].

Corydaline, in contrast to its 13-epimer mesocorydaline, shows the so-called BOHLMANN bands[5] in its IR-spectrum indicative of a *trans*-quinolizidine. This evidence, in conjunction with the fact that these bases undergo Hofmann degradation to afford characteristically different products, has been interpreted by BERSCH in favor of a *cis* 13, 14-configuration.

Isomer (1) can be represented by three conformations (1a–1c). Conformation (1a), possessing a *trans*-quinolizidine ring juncture is anticipated to be the most stable and therefore, from its predominance at equilibrium, compounds in this series would be expected to exhibit BOHLMANN bands in their IR-spectra. Isomer (2) in which the 13, 14-hydrogens are *trans* can similarly be represented by the three conformations (2a–2c). However, in this case the *trans*-quinolizidine conformation is destabilized by an energetically unfavorable non-bonded interaction of the 13-methyl hydrogens with the 1-hydrogen. Consequently, the most stable conformation is likely to be one of the *cis*-quinolizidine forms (2b or 2c) in which this steric compression is relieved. Hence, the





[1] Protoberberine alkaloids, Part 1.

[2] H. W. BERSCH, Archiv. der Pharm. *291*, 595 (1958).

[3] Y. KONDO, J. pharm. Soc. Japan *83*, 1017 (1963).

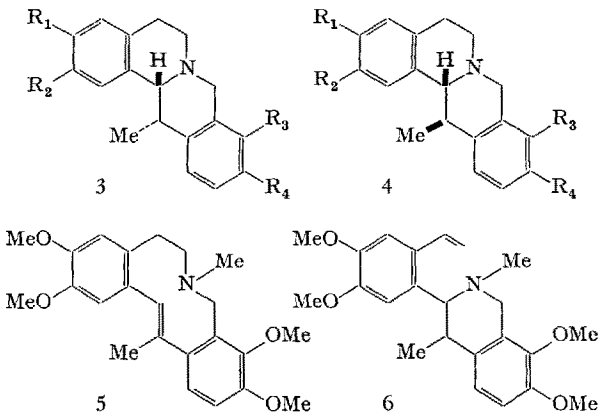
[4] Although the conclusions reached by BERSCH were essentially correct, the arguments used were, in parts, invalid and the portrayal of the various conformations discussed was unclear. In view of the rejection of KONDO's alternative proposal for the stereochemistry of corydaline here presented, and the later extension (vide infra) of arguments based on conformational analysis which lead to configurational assignments of related alkaloids, a statement of the factors involved is warranted.

[5] F. BOHLMANN, Chem. Ber. *91*, 2157 (1958); *92*, 1798 (1959). – E. WENKERT and D. K. ROYCHAUDHURY, J. Am. chem. Soc. *78*, 6417 (1956).

IR-spectrum of this isomer would not be expected to exhibit Bohlmann bands.

IR-spectral data alone may then prove a useful criterion for stereochemical assignments at the C(13) and C(14) positions in this group of alkaloids. It was essentially on these grounds that BERSCH assigned corydaline as structure 3, $R_1 = R_2 = R_3 = R_4 = OMe$, and mesocorydaline as structure 4, $R_1 = R_2 = R_3 = R_4 = OMe$.

Further evidence for these assignments has been cited[2] from the differing course of Hofmann degradation of corydaline and mesocorydaline. Corydaline affords the 10-membered-ring system 5, resulting from cleavage of the C(14)-nitrogen bond whereas mesocorydaline yields the methine 6. Inspection of models reveals that only isomer 1 can attain a *trans*-anticoplanar arrangement (in both conformations 1a and 1b) of the necessary centers involved for a concerted elimination which would result in a facile cleavage of the C(14)-nitrogen bond[6].



KONDO's arguments for a *trans*-arrangement of the 13,14-hydrogens in corydaline are based on the following evidence. Oxidation of corydaline with mercuric acetate affords dehydrocorydaline which on reduction with borohydride regenerates the starting alkaloid. These results, in conjunction with the presence of BOHLMANN bands in the IR-spectrum of the alkaloid, were taken as being evidence of structure 2 for corydaline[7]. In addition, the chemical shift of the 13-methyl group was cited as lending further support for this proposed structure[8].

The presence of BOHLMANN bands in corydaline and its representation as structure 2 are inconsistent with the results of conformational analysis (vide supra) and the NMR data is inadmissible owing to the vastly different environments of the methyl group in corydaline and that in the simple quinolizidine with which the comparison was made. These arguments constitute sufficient reasons to reject the stereochemical proposals made by KONDO.

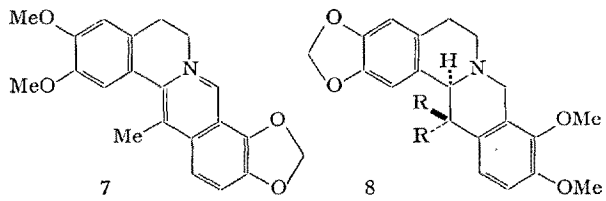
Stereochemical assignments can now be made for the remaining known 13-methyl substituted bases of the tetrahydroprotoberberine group.

The stereochemistry of corybulbine (3; $R_1 = OH$, $R_2 = R_3 = R_4 = OMe$) and isocorybulbine (3; $R_2 = OH$, $R_1 = R_3 = R_4 = OMe$) is defined as shown by their direct conversion to corydaline on methylation[2]. Thalictricavine (3; $R_1 = R_2 = CH_2$(O–O), $R_3 = R_4 = OMe$) must have the stereochemistry shown in view of its reported[9] conversion to corydaline.

The alkaloid Base II described by TAGUCHI and IMASEKI[10] may be formulated as the 13-epimer of thalictrofoline since both yield dehydrothalictrofoline (7) on oxidation. The assignment of Base II to the 13,14-*cis*-series is possible on the basis of its reported[10] conversion to corydaline.

Consistent with the stereochemical assignments of these alkaloids is the fact that all are reported[2,10] to exhibit absorptions in the region of 2800 cm^{-1}. Further support for the 13,14-*cis* configuration for thalictricavine is available from its reported[11] conversion to the 10-membered-ring base 5 (CH_2(O–O) at the 2,3-position instead of OMe's).

The assignment of the 13,14-*cis* configuration to Base II is sufficient to define the stereochemistry of thalictrofoline (4; $R_1 = R_2 = OMe$, $R_2 = R_4 = CH_2$(O–O)) as portrayed in view of the above-mentioned relationship between these alkaloids. Confirmatory evidence for the stereochemistry of thalictrofoline is available from its reported[11] conversion to mesocorydaline[12]. Thus, thalictrofoline is identified as the sole naturally occurring base known so far in this series to possess a C(13)-C(14) *trans* configuration.



Absolute configuration. The absolute configuration of tetrahydroprotoberberine alkaloids which are not substituted at the 13-position has been determined by CORRODI and HARDEGGER[13]. A negative rotation or a negative Cotton effect in this group of alkaloids has been shown[14] to correspond to a 14α-hydrogen configuration.

[6] The statement[2] that one of the *cis*-quinolizidine conformations of the C(13)-C(14) *trans* isomers possesses the necessary coplanarity of the C(13)-hydrogen and the C(14)-nitrogen bond is probably incorrect. Examination of Dreiding models reveals that the closest approach to coplanarity of these centers is in conformation 2a, in which the deviation from coplanarity is as large as ca. 35°.

[7] The apparent rational for this proposal was the fact that borohydride reduction was expected to give the most stable product, which was assumed to be the structure in which the C(13)-methyl was equatorial as claimed in structure 2. Whether borohydride can be expected to lead to the more stable product is uncertain; in any event the thermodynamically more stable system is undoubtedly structure 1 and not its 13-epimer. Whatever the course of the reduction the conclusions based on such arguments must be considered invalid.

[8] The chemical shift of the C(13)-methyl was similar to that reported for 1(eq)-methylquinolizidine (T. M. MOYNEHAN, K. SCHOFIELD, R. A. Y. JONES, and A. R. KATRITSKY, J. chem. Soc. *1962*, 2637).

[9] R. H. F. MANSKE, J. Am. chem. Soc. *75*, 4928 (1953).

[10] H. TAGUCHI and I. IMASEKI, J. pharm. Soc. Japan *84*, 955 (1964).

[11] C. TANI, N. TAKAO, S. TAKAO, and K. TAGAHARA, J. pharm. Soc. Japan *82*, 751 (1962).

[12] R. H. F. MANSKE, Can. J. Res. *21B*, 111 (1943).

[13] H. CORRODI and E. HARDEGGER, Helv. chim. Acta *39*, 889 (1956).

[14] G. G. LYLE, J. org. Chem. *25*, 1779 (1960). – See also A. BROSSI, M. BAUMANN, F. BURKHARDT, R. RICHIE, and J. R. FREY, Helv. chim. Acta *45*, 2219 (1962).

The introduction of an additional center of asymmetry at the 13-position in this ring system does not appear to affect the sign of rotation when the group introduced is hydroxyl; both (−)-ophiocarpine (8; R = H, R′ = OH) and (−)-13-epiophiocarpine (8; R = OH, R′ = H), having the absolute configuration portrayed, show negative rotatory dispersion curves[15] in common with (−)-canadine (8; R = R′ = H).

The highly polarizable hydroxyl group at the 13-position makes only a small contribution to the molecular rotation (M_D = ca. 1120°) of the tetrahydroprotoberberine ring system (ΔM_D 13αOH = + 7° ΔM_D β13OH = + 113°). Thus this asymmetric center in the 13-methyltetrahydroprotoberberines is likely to make even less of a contribution to the molecular rotation[16]. However, in contrast to the 13-methyl series, both ophiocarpine and 13-epiophiocarpine exist in the *trans*-quinolizidine conformation and, as such, the extension of molecular rotational and optical rotatory dispersion data should be valid for corydaline and related alkaloids but may not be so for the conformationally distinct mesocorydaline series. The naturally occurring forms of corydaline, corybulbine, isocorybulbine Base II and thalictricavine all have positive rotations; therefore the structures portrayed for these alkaloids represent their absolute configurations.

Zusammenfassung. Die stereochemische Zuordnung des Alkaloids Corydalin gelang auf Grund von konformationsanalytischen und spektroskopischen Daten. Grundsätzliche Überlegungen, unter Berücksichtigung gewisser chemischer Beziehungen, erlauben die stereochemische Zuordnung für Corybulbin, Isocorybulbin, Base II, Thalictracavin und Thalictrofolin.

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Department of Chemistry, Duke University, Durham (North Carolina USA), August 2, 1965.

[15] M. OHTA, H. TANI, and S. MOROZUMI, Chem. pharm. Bull. *12*, 1072 (1964).

[16] J. H. BREWSTER, Tetrahedron *13*, 106 (1961).

The Taste of L- and D-Amino Acids

Free amino acids often occur in foods in relatively high amounts, largely as a result of the mode of preparation prior to consumption. Therefore, free amino acids are certainly of importance for the taste of dietary preparations.

However, only few and often controversial data are available on the taste of amino acids. This is probably due to the fact that the L- and D-amino acids are often different in taste, and that this has not been considered in a suitable manner in many investigations.

However, the first recorded observation of differences in physiological response to the L- and D-amino acids pertained to their effect on taste[1]; nowadays, the D-enantiomorphs are generally considered to be sweet compared to the corresponding L-enantiomorphs which have usually been described as tasteless or bitter[2–7]. However, no precise data are available in this respect. A well-known exception is glutamic acid; its special flavour effect has been investigated in detail[8,9].

It was therefore our aim to determine the taste of free L- and D-amino acids in comparison with standard substances of a known taste; the investigations were conducted on the basis of statistical tasting tests.

Eighteen amino acids, listed in Table I, were tested. The L- and D-enantiomorphs were obtained from Mann Research Laboratory, New York (USA), in pure form, chromatographically tested and with their specific rotation indicated and controlled in our laboratory. For arginine, proline and cysteine, the D-enantiomorphs were unavailable in pure form, so the racemic mixtures were used instead. D-histidine was prepared from D-histidine HCl by electrodialysis[10] prior to testing.

For the tests, a taste panel was devised comprising 8–12 persons having average taste sensitivities. Persons with deviating sensitivities, about one-fifth of all the individuals tested, were not accepted.

In an initial series of tasting tests, all the amino acids were tasted in 0.3% aqueous solutions, adjusted to pH 6.0 by NaOH or HCl, with a smaller test group, in order to obtain general characteristics of the different tastes. The concentration of 0.3% was chosen for all tests as a realistic concentration, permitting an evaluation of all amino acids at the same level.

The taste characteristics are described in Table I. Three groups of amino acids were formed. Group 1 consists of 8 amino acids whose L- and D-enantiomorphs have no taste at all or only a barely perceptible taste. This group was excluded from further tests due to its taste neutrality. Group 2 consists of three amino acids whose L- or D-enantiomorphs have such a complex taste that they cannot be evaluated in relative tasting tests. Therefore, these compounds were also excluded from further tests. This group contains the unique glutamic acid and the sulphur-containing amino acids. The latter presumably always form decomposition products, which are responsible for their sulphurous-meaty taste but are not related to the original amino acid structure.

Finally, group 3 comprises seven amino acids with distinctive tastes, either bitter or sweet, and their taste was

[1] A. PIUTTI, C. R. Acad. Sci. Paris *103*, 134 (1886).

[2] E. C. CROCKER, in *Monosodium Glutamate* (Ed., W. F. DOVE; Food and Container Institute, Chicago 1948), p. 25.

[3] S. L. GALVIN, in *Monosodium Glutamate* (Ed., W. F. DOVE; Food and Container Institute, Chicago 1948), p. 39.

[4] C. P. BERG, Physiol. Rev. *33*, 145 (1953).

[5] A. MEISTER, *Biochemistry of the Amino Acids* (Academic Press, New York 1957), p. 76.

[6] L. N. FERGUSON and A. R. LAWRENCE, J. chem. Education *35*, 436 (1958).

[7] A. R. LAWRENCE and L. N. FERGUSON, Nature *183*, 1469 (1959).

[8] W. F. DOVE, *Monosodium Glutamate* (Food and Container Institute, Chicago 1948).

[9] R. H. WALTERS and C. R. ISKER, *Monosodium Glutamate* (Food and Container Institute, Chicago 1955).

[10] D. M. GREENBERG and M. ROTHSTEIN, in *Methods in Enzymology* (Ed., S. P. COLOWICK and N. O. KAPLAN; Academic Press, New York 1957), vol. 4, p. 676.