Chiroptical Properties of (+)-Corycavine and Corycavamine

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The resolution of racemic corycavine via its (+)-10-camphorsulfonate, the equivalency of (+)-corycavine and corycavamine, as well as the racemization of (+)-corycavine are described. 13R-Configuration is assigned to (+)-corycavine, based on CD data.

Optical Resolution of 1 and Identification with Corycavamine

The resolution of racemic corycavine (1) is important for comparison with the optically active corycavamine (2), for which data are available.

(+)-Corycavine (1) and corycavamine (2) (Scheme 1) were isolated from Corydalis cava (tuberosa), papaveraceae, in 1894 and 1902, respectively. The structure of these alkaloids was proposed by von Bruckhausen in 1925 as 1, indicating that these compounds are protopine type alkaloids. V. Bruckhausen termed the optically inactive form, m.p. 217-218°C corycavine (1), while the optically active form with a specific rotation of +166.6° (m.p. 148-149°C) is termed corycavamine (2).

Crystallographic data presented in our previous paper demonstrated that corycavine (1) exactly fits the "racemic form." Several reports concerning the isolation of (±)-corycavine (1) have been described. However, since Gadamer's description, we have not seen lit. regarding the isolation of corycavamine (2). In general, it seems relatively unique for naturally occurring alkaloids bearing an asymmetric C-atom to be isolated as a racemate only. Further, the lit. cited above also described racemization occurring from heating with acetic anhydride at above 180°C. One can, therefore, presume that corycavine (2) converts to (±)-corycavine (1) relatively easily through usual isolation treatment.

In biosynthesis, protopine type alkaloids are key intermediate to benzo[c]phenanthridine type (sanguinarine, etc.), and to hydrobenzo[c]phenanthidine type (corynoline and chelidonine, etc.), having pharmacological significance. The relationship between the absolute configurations of both types tells us what kind of enzymatic reaction mechanism takes place at the ring reconstitution stage. Thus, it seemed important to investigate further the absolute configuration and chiroptical properties of protopine type alkaloids.

The present paper deals with the optical resolution of (±)-corycavine (1), and the measurement of racemization of (+)-corycavine (2), by the circular dichroism (CD) method and by H-NMR spectroscopy, as well as a consideration of the absolute configuration of (+)-corycavine (2) and its derivatives by CD.

\[ \text{Residual [\theta] intensity \% = [\theta]_x \text{ value at } x \text{ min after/initial [\theta] value \times 100.} \]

Fig. 1 The rate of racemization of 3. Residual [\theta] intensity \% = [\theta] value at x min after/initial [\theta] value \times 100.
specific optical rotation of 2 and 3 were not altered by re-crystallization. 2) The IR-spectrum of 2 in KBr substantially agreed with the spectrum of 3, but did not agree with the spectrum of 1. All three spectra agreed in solution. 3) The CD-spectra of 2 and 3 are also equal in intensity though opposite in sign. Melting point, crystal form, specific optical rotation, etc. of 2 prepared in this way agreed very closely with those of corycavamine described by Gadamer. Consequently, one can conclude that corycavamine is identical with (+)-corycavine (2) with 100% optical purity.

Measurements of Racemization of 2 and 3

The chiral center C-13 in 2 is located in the α-position of the keto group and in benzyl-position. Consequently, racemization of 2 is believed to be relatively easy. In order to study this racemization, the rate was investigated under alkaline conditions generally used for isolation of alkaloids from various plants.

The time-course of CD-band intensities at 286 nm of 3 was measured in ethanolic NaOH at 20°C. The rate of remaining optical activity of 3 was calculated by use of the value [β] at 286 nm, and the slope for the data was determined by the least-squares method (Fig. 1). The rate of racemization of 3 was 5.96 x 10^-2 min^-1 and the half-life period was 11.6 min. The similarity of this value to that of (-)-1,2-diphenyl-propan-1-one suggests that the racemization rate of 3 is due to its having in part the same structure.

From the ^1H-NMR results, furthermore, we elicited information about the racemization of 2. All proton resonances in CDCl3 have been assigned. The spectrum (Fig. 2a) displayed the methyl protons (C-13H-CH3) as a doublet with J = 7 Hz at δ = 1.36. By addition of NaOD in CD3OD this doublet collapsed to a singlet at δ = 1.36 (spectrum b); after 3 h, the spectrum c showed only the deuterated species. This phenomenon is due to the disappearance of the proton coupling (C-13D-CH3). The ^1H-NMR spectra indicate that the asymmetric carbon atom C-13 of 2 bears a readily ionizable hydrogen atom which exchanges easily H against D.

These results show that optically active 13-substituted protopine type alkaloids are rapidly converted into racemates under mild alkaline conditions. This suggests that, if isolation from plants is meticulously carried out, the optically active form in the corycavine/corycavamine fraction may be obtained. The isolation of naturally occurring 2 from Corydalis incisa and Corydalis cava was studied again. The examination showed that 2 comprises 60% in the 1 and 2 fraction from Corydalis incisa and 14% from C. cava plants.

Relationship between CD-Spectra and the Absolute Configuration of 2 and its Derivatives

The CD-spectrum of 2 is of interest in connection with the absolute configuration of the asymmetric C-13 atom. While the ORD- and CD-spectral investigation of protoberberine type alkaloids has been reported in several papers, no study has been reported on the chiroptical discussion of protopine type. Earlier work had shown that for 1, in spite of a ten-membered ring system with one rigid conformation in solution, direct use of the empirically CD-spectral rule derived from protoberberine type compounds for corycavine was problematic. Consequently, 2 was converted into a protoberberine by reductive ring closure, and the CD-spectrum of that derivative was also investigated.

The protopine skeleton of (+)-corycavine was transformed to a protoberberine skeleton as follows (Scheme 1): Reduction of 2 with LiAlH4 gave the optically active (+)-dihydro-
corycavine (4). 4 was treated with aqu. HCl, followed by addition of KI. The ring closure product was identical with (+)-meso-terahydrocorysamine N-methiodide (5).

The CD-spectra of 2, 3, and 4 are shown in Fig. 3. The curve for 2 shows from the side of the long wave length positive and negative maxima in α-band (around 290 nm), in β-band (at = 240 nm) and in β-band (at = 200 nm). The curve of 3 is the mirror-image of 2. A striking characteristic of the spectra of 2 and 3 is the high amplitude of the Cotton effect near 200 nm in 4 may be attributed to the conformational change of ring B, due to the flexibility of this ten-membered ring.

It is known that protonation of protopine type alkaloids leads to a quaternary form similar to the quaternary methiodides of protoberberine type alkaloids. The preferred conformation of the salt of 2 may be the cis-quinoilizidine system, in order to avoid the steric hindrance between the C-13-methyl group and the two protons at C-1 and C-12. This is also confirmed by the NMR study. The CD-spectra of the TFA salt of 2 and 5 are shown in Fig. 5. Each compound has two asymmetric carbons and an asymmetric N-atom and they differ only in the substituent at C-13a. Both curves have intrinsically similar CD properties. From a consideration of the whole spectral pattern and from a comparison of the CD data with that of other protoberberine type alkaloids, it seems most reasonable to conclude that the absolute configuration of the salt of 2 must be assigned as 7N(β), 13α(S), and 13a(S).

Therefore, the absolute configuration of 2-base must be assigned as 13(R).

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Experimental Part

General Remarks

Melting points: Kofler hot stage apparatus, uncorrected. IR spectra: EPI-C2 (Hitachi), nujol, KBr pellets, CHCl3 solution. Mass spectra: JEOL-DIS. 1H-NMR spectra: Varian-XL-200 (200 MHz, FT-mode), TMS as internal standard. Coupling constants J in Hz. Optical rotations: DIP-SL (JASCO) polarimeter. CD spectra: ORD/UV-5 and CD-J-500C (JASCO), data were measured at ca. 3 x 10⁻⁴ mol/l, 20°C in cells of 0.1-5 mm path lengths.

1. Optical resolution of (±)-corycavine (1)

To a solution of 1 (157 mg) in methanol was added a solution of (+)-camphorsulfonic acid (100 mg) in methanol. After removal of the solvent, the remaining residue gave the (±)-corycavine (+)-camphorsulfonate, m.p.
273-275°C. The salt was recrystallized from a mixed solvent (methanol, acetone, ether) three times for 12 h at room temp, to give (+)-corycavine (→-corycavine sulfate) (40 mg) as colorless plates, m.p. 282-287°C. The crystals were dissolved in H2O (50 ml). The aqueous solution was made faintly alkaline to litmus with 5% NH4H2O and extracted repeatedly with ether (2 x 20 ml). The org. phase was washed with saturated NaCl solution (2 x 20 ml), dried with Na2SO4 and evaporated in vacuo. The residue was crystallized from ether/petroleum ether to give 24 mg of (+)-corycavine: transparent needles, m.p. 219-220°C, [α]D 5 +43.0° (c = 0.7, CHCl3). IR: ν max (Nujol) 1665 cm⁻¹. EIMS: 369 (M+ 1), 206 (16), 163 (31), 162 (100). C21H21O3N (369.1) Calcd. C 68.6 H 5.76 N 3.8 Found C 68.5 H 5.84 N 3.7.

3. Preparation of (+)-Dihydrocorycavine

Crystallization from methanol gave colorless columns, m.p. 219-220°C. EIMS: 369 (M+ 1), 206 (16), 163 (31), 162 (100). C21H21O3N (369.1) Calcd. C 68.6 H 5.76 N 3.8 Found C 68.5 H 5.84 N 3.7.

4. (+)-Mesotetrahydrocorysamine N-methiodide

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References

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