ALKALOIDS FROM *Corydalis cava* (L.) SCHW. *et* KOERTE*

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From the tubers of *Corydalis cava* (L.) SCHW. et KOERTE the following alkaloids were isolated: (+)-bulbocapnine, (+)-corydaline, (+)- and (±)-tetrahydropalmatine, (+)- and (±)-thalictricavine, (+)-corybulbine, corycavine, protopine, (+)-corypalmine, (±)- and (+)-isocorypalmine, (+)-corytuberine, (+)-corydine, (+)- and (±)-corycavidine, (+)-canadine, (+)-stylopine, (−)-scoulerine, capnoidine, dehydrocorydaline, corysamine, coptisine; further the following alkaloids not yet described as components of this plant: (+)-tetrahydrocorysamine, allocryptopine, palmatine, berberine, dehydrocorybulbine, dehydrothalictricavine, (+)-α-stylopine methohydroxide and the alkaloid CC2, as well as the new natural alkaloids dehydroapocavidine, (+)-bulbocapnine methohydroxide, and α-tetrahydrocorysamine methohydroxide. Further the presence of apocavidine, columbamine, jatrorrhizine and magnoflorine was also proved. In the aerial parts (+)-bulbocapnine, (+)-stylopine, protopine, capnoidine, glaucine, domestine, alkaloid CCI (probably dehydrodomestine), predicentrine, isoboldine, corydine, coptisine, corysamine and traces of bulbocapnine methohydroxide were found.

Corydalis cava (L.) SCHW. et KOERTE (synonymum *C. tuberosa* DC.) from the subfamily *Fumarioideae*, section *Radix-cava* IRM., is one of the most widely distributed species of the genus *Corydalis*, growing in Czechoslovakia. The tubers of this plant represent a very rich source of various alkaloids of which about thirty have been isolated and characterized so far (for a literature review see refs.[1-3]). In connection with the discovery of important pharmacodynamic properties of some aporphine and protoberberine alkaloids[4,5] the alkaloids from *C. cava* are becoming more and more interesting for medicinal purposes. Although the alkaloids from the aerial parts of this plant were recently studied in detail[6]** no attention has so far been devoted to the alkaloids from the tubers of Czechoslovak origin. The presence of quaternary alkaloids in tubers was also almost unknown.

In this paper we present the results of the study of the alkaloids of two plant samples collected from two different localities in the surroundings of Brno. From this material we managed to isolate altogether thirty seven individual alkaloids

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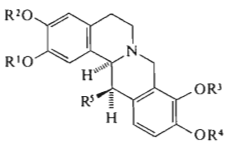
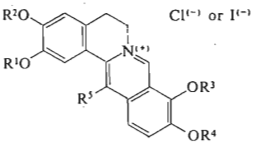
** According to a private communication from Dr V. Preininger the material used in paper[6] consisted of aerial parts of the plant exclusively.

and to identify of further six. From the tubers we obtained 4·82% (sample 1) and 4·21% (sample 2) of total alkaloids which we separated using the method currently used in our laboratory. From the fraction of tertiary bases (4·72% and 3·86 of the tubers) we isolated (+)-bulbocapnine as the main alkaloid. Using either direct crystallization or chromatography on alumina we obtained lesser amounts of (+)--corydaline (*Ia*), (+)- and (±)-tetrahydropalmatine (*Ie*), corycavine, (+)-thalictricavine (*Ib*), (+)-corybulbine (*Id*), (+)-corypalmine (*Ii*), (+)-isocorypalmine (*Ih*), (+)- and (±)-corycavidine, (+)-corydine, (+)-canadine (*If*), (+)-stylopine (*Ig*) and capnoidine, the presence of which in the tubers was already known. The mass spectrum of corycavidine, very probably not yet published, with the ions at *m/e* 383 (M^+), 220, 178 (*c*, base peak; $R^1 = R^2 = CH_3$) and 163 is typical of the fragmentation of the alkaloids of the protopine type[7]. We have further isolated protopine, not yet described in tubers and known to be present in the aerial parts of *C. cava* only, then (±)-thalictricavine, (±)-isocorypalmine, (−)-scoulerine (only the (+)-form, *Ij*,



I

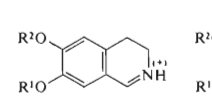


II

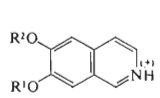
a: $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
b: $R^1 + R^2 = CH_2$, $R^3 = R^4 = R^5 = CH_3$
c: $R^1 + R^2 = R^3 + R^4 = CH_2$, $R^5 = CH_3$
d: $R^1 = R^3 = R^4 = R^5 = CH_3$, $R^2 = H$
e: $R^1 = R^2 = R^3 = R^4 = CH_3$, $R^5 = H$
f: $R^1 + R^2 = CH_2$, $R^3 = R^4 = CH_3$, $R^5 = H$
g: $R^1 + R^2 = R^3 + R^4 = CH_2$, $R^5 = H$
h: $R^1 = R^5 = H$, $R^2 = R^3 = R^4 = CH_3$
i: $R^1 = R^3 = R^4 = CH_3$, $R^2 = R^5 = H$
j: $R^1 = R^3 = R^5 = H$, $R^2 = R^4 = CH_3$
k: $R^1 = H$, $R^2 = R^5 = CH_3$, $R^3 + R^4 = CH_2$

has been found in the tubers so far), allocryptopine and (+)-tetrahydrocorysamine (*Ic*). The two last mentioned alkaloids were isolated from *C. cava* for the first time. Several years ago tetrahydrocorysamine was isolated by Japanese authors from *C. pallida* var. *tenuis* YATABE[8] in the (+)-form, and from *C. incisa* (THUNB.) PERS.[9] in the (−)-form. We have identified the alkaloid isolated from the tubers of *C. cava* on the basis of its mass spectrum, IR and UV spectrum and TLC, by comparison with (±)-tetrahydrocorysamine prepared by reduction of corysamine[10]. The mass

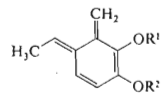
spectrum contained the following characteristic ions: *m/e* 337 (M^+), 176 (*a*), 174 (*b*) and 162 (*c*, base peak; in all instances $R^1 + R^2 = CH_2$). All the 13-methyltetrahydroprotoberberines isolated from the tubers of *C. cava* displayed Bohlmann's bands in the 2700–2800 cm^{-1} region of the IR spectrum, indicating the *cis* position of the hydrogen atoms on $C_{(13)}$ and $C_{(14)}$ and the quinolizidine system in *trans* conformation[11,12]. A further tertiary alkaloid, (+)-corytuberine, was obtained from the fraction of bases extractable with chloroform, or more rationally, by extraction with chloroform after conversion to hydriodide[13].



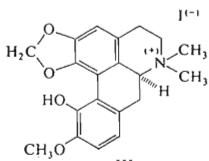
a



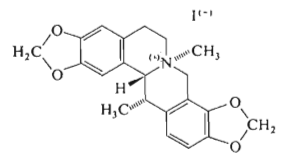
b



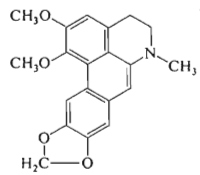
c



III



IV



V

From the fraction of quaternary non-phenolic protoberberines of sample 1 (0·073%) we separated in the form of chlorides dehydrocorydaline (*IIa*) as the main component, the presence of which has been described earlier[14], and dehydrothalictricavine (*IIb*) which was identified by comparison with a preparation obtained on oxidation of thalictricavine *i.e.* by IR and UV spectra, m.p. and mixture m.p. and chromatographically. Smaller amounts of corysamine (*IIc*) and palmatine (*IIe*) were also isolated and the presence of a small amount of berberine (*IIf*) and coptisine (*IIg*) demonstrated. None of these four alkaloids have been found in the tubers of *C. cava* so far. The same fraction from sample 2 (0·156%) contained palmatine as the main component, then a smaller amount of corysamine, coptisine and berberine, and only traces of dehydrocorydaline.

From the fraction of the iodides of quaternary alkaloids we isolated a new alkaloid as the main component, which we identified on the basis of its UV and IR spectrum, optical rotation value, m.p. and mixture m.p. and chromatographic behaviour as (+)-bulbocapnine methiodide (*III*) by direct comparison with a sample prepared from (+)-bulbocapnine. From the same fraction we also isolated very small amounts of (+)-α-stylopine methiodide and a further alkaloid, identified by mass spectrum and R_F values as α-tetrahydrocorysamine methiodide (*IV*). The latter was prepared from tetrahydrocorysamine for comparison.* As further alkaloids we separated from this fraction dehydrocorybulbine iodide (*IId*) and dehydroapocavidine iodide (*IIk*). On reduction of the latter alkaloid with sodium borohydride (±)-apocavidine[12] (*Ik*) was obtained. Its mass spectrum contained characteristic ions at *m/e* 339 (M^+), 204, 178 (*a*), 176 (*b*, in both cases $R^1 = H$, $R^2 = CH_3$) and 162 (*c*, base peak; $R^1 + R^2 = CH_2$). After labelling deuterium was found in the ion M^+, *a* and *b*. Tetrahydrocorysamine methohydroxide and dehydroapocavidine have not been found as natural alkaloids so far. From the mother liquors a negligible amount of the iodide of the quaternary alkaloid labelled CC2 was isolated. It could be characterized by m.p. 162°C and R_F values only. The presence of a small amount of jatrorrhizine (*IIi*), columbamine (*IIh*), magnoflorine and several additional unidentified alkaloids was also proved.

The alkaloids from the aerial part (0·46% and 0·84%) were studied for the sake of orientation only, and practically the same alkaloids were found as in paper[6], *i.e.* bulbocapnine, protopine, stylopine, capnoidine, domestine (nantenine), predicentrine, isoboldine, coptisine and corysamine. In addition to this we also found glaucine, isolated earlier[20], then corydine, trace amounts of bulbocapnine methiodide and several other unidentified alkaloids. In addition to this we also isolated negligible amounts of the non-phenolic aporphine alkaloid labelled CCl, which according to its composition $C_{20}H_{19}NO_4$ and in view of the simultaneous presence of domestine is very probably dehydrodomestine (dehydronantenine, *V*). This alkaloid was recently detected in *Nandina domestica* THUNB.[21] using gas chromatography–mass spectrometry. In the aerial parts and in the tubers we also observed the presence of 1,2-methylenedioxy-6a,7-dehydroaporphine-10,11-quinone which was isolated from the aerial part of *C. cava*[6]. This blue coloured substance is, however, an artifact which is demonstrably formed on air oxidation of solutions of bulbocapnine.

* On methylation of tetrahydrocorysamine with methyl iodide two stereoisomeric methiodides are formed[15,16], named α-form (B/C *cis*) and β-form (B/C *trans*; *cf.*[17]), differing distinctly by their R_F values in paper chromatography, as observed already in metho-salts of other tetrahydroprotoberberines[18]. In the literature[15] only both stereoisomeric methochlorides of (±)-tetrahydrocorysamine have been described so far. The alkaloid isolated from *C. cava* is probably the (+)-enantiomer. According to its m.p., 266°C, (±)-tetrahydrocorysamine methiodide mentioned in ref.[19] is evidently the α-form (see Experimental). See also note added in proof.

From a comparison of the results of a study of samples 1 and 2 it follows that the composition of the alkaloids from both samples practically does not differ qualitatively; substantial differences were, however, observed in the relative ratio of individual alkaloids, which was especially striking in tubers. While the ratio between the $C_{(13)}$--methylated and $C_{(13)}$-nonmethylated tetrahydroprotoberberines was in the tubers of sample 1 about 1 : 0·6, it was 1 : 5·5 in sample 2. Similar differences were observed between the tubers of North-German origin, studied by Schmidt and Gadamer (for a very extensive literature survey see for example ref.[1]), in which practically only $C_{(13)}$-methylated alkaloids were found, and the tubers from Wienerwald[22,23] which contained predominantly $C_{(13)}$-nonmethylated tetrahydroprotoberberines. This difference in our samples was still more pronounced with respect to the composition of quaternary protoberberines, mentioned above. These differences are evidently due to the existence of different chemotypes in the *C. cava* species. In contrast to this substantially higher yields of quaternary alkaloids from the tubers of sample 2 can be rather attributed to use of a more suitable isolation method than was used in the case of sample 1.

EXPERIMENTAL

The melting points were determined on a Kofler block and they were not corrected. The mass spectra were measured on a AEI-MS 902 spectrometer, the IR spectra (in KBr) on a spectrophotometer Zeiss UR 10 and the UV spectra (in methanol) on a Unicam SP 1800 instrument. For thin layer chromatography both silica gel G (Merck) with the solvents cyclohexane–diethylamine 9 : 1 (S_1), cyclohexane–chloroform–diethylamine 7 : 2 : 1 (S_2) and 6 : 3 : 1 (S_3), methanol (S_4), methanol–25% ammonia 200 : 1 (S_5), ethanol–water–25% ammonia 15 : 9 : 1 (S_6), methanol–water–25% ammonia 15 : 3 : 1 (S_7) and 1-propanol–water–85% formic acid 12 : 7 : 1 (S_8), and Silufol UV 254 plates (Kavalier, Votice) with the systems methanol–diethylamine 4 : 1 (S_9) and 1 : 1 (S_{10}). Paper chromatographies were carried out in descending manner on paper Whatman No 1 in the system 1-butanol–acetic acid–water 10 : 1 : 3 (S_{11}) and ethanol–water 3 : 2 (S_{12}). The spots of fluorescing alkaloids were inspected under the UV lamp, and the spots of other alkaloids were detected with potassium iodoplatinate (TLC) or Dragendorff's reagent (paper).

Extraction and Isolation of Alkaloids

The plants were collected at the stage of unripe fruits from a natural locality, both in a swampy forest south of Brno, on 13. 5. 1958 (sample 1), and on bushy highlands north-west of Brno, on 5. 5. 1977 (sample 2). The tubers and the aerial parts were separated and dried at room temperature. From the dry residue of whole plants of sample 1 or 2 the tubers represented 74% or 70% of the weight, respectively. In both cases the tubers were worked up immediately after drying, so that a possible oxidation of tetrahydroprotoberberines with air oxygen would be prevented as far as possible.

Alkaloids from Tubers

Dry ground tubers of sample 1 (1192 g) were extracted in a Soxhlet extractor with ethanol. From the extract saccharose crystallized out (6·5% of the tubers). Ethanol was then distilled off, the residue dissolved in water and extracted with ether (fraction *L*). The small amount of alkaloids that passed into the ethereal layer was extracted with 5% sulfuric acid and the solution was added to the aqueous layer. This was alkalized with sodium carbonate and extracted with ether (fraction *A*) and chloroform (fraction *E*), then strongly alkalized with sodium hydroxide (pH > 13) and reextracted with ether (fraction *B*). Since the remaining aqueous layer still gave a positive reaction for alkaloids, it was neutralized with hydrochloric acid, concentrated on a water bath to about 1 l volume, filtered, additioned with picric acid, and the precipitate formed filtered off under suction (fraction *P*).

From the ethereal solution of the fraction *L* 51 mg of a compound crystallized out, m.p. 285—295°C (chloroform–methanol), of nonbasic character, which was not further studied. Evaporation of the mother liquors gave 8·36 g of a fatty oil which partly crystallized.

The bases of fraction *A* (49·77 g; 4·18%) were dissolved in dilute hydrochloric acid and separated in the usual manner[24,25] to a fraction of hydrochlorides extractable with chloroform (*AC*) and another non-extractable (*AD*). Both fractions were further separated to non-phenolic bases (*ACa* and AD_1) and phenolic bases (*ACb* and AD_2). On crystallization from dilute hydrochloric acid the bases *ACa* (14·45 g) afforded a mixture of poorly soluble hydrochlorides from which corydaline (3·69 g), (+)-tetrahydropalmatine (2·51 g), (±)-tetrahydropalmatine (0·74 g) and (+)-stylopine (52·7 mg) were obtained after previous conversion to bases (8·06 g) by crystallization from ether and ethanol. The residue (0·29 g) consisted of a semicrystalline mixture of corydaline and tetrahydropalmatine and 0·17 g of their oxidation products (dehydrocorydaline and palmatine), formed artificially. The bases obtained from the filtrate after poorly soluble hydrochlorides were crystallized from ether and ethanol to afford 2·90 g corydaline, 0·89 g of thalictricavine, 0·08 g of corycavine, 0·07 g of a crystalline mixture of corydaline, tetrahydropalmatine and thalictricavine, and 1·47 g of an amorphous residue. From the bases AD_1 (5·02 g) the main fraction of corycavine, protopine and corycavidine were separated by crystallization from chloroform–ethanol. From the remaining mixed fractions (including mixed fractions 32—40 from column chromatography, see below) poorly soluble hydrochloride of corycavine was obtained by crystallizations from dilute hydrochloric acid, while the residue was separated by crystallization from chloroform–methanol. Thus a total of 2·19 g of corycavine, 0·32 g of protopine, 0·17 g of corycavidine and 0·06 g of a crystalline mixture was obtained. The rest was 1·08 g of amorphous bases and 0·31 g of oxidation products. As according to TLC the amorphous residues of bases from *ACa* and AD_1 had the same composition, they were pooled and purified from the decomposition products and separated by column chromatography on alumina. The column was prepared from 105 g of alumina according to Brockmann (Reanal), activity about II, using benzene–light petroleum 1 : 1. The bases (1·82 g) were applied into the column in 60 ml of the same mixture. The volume of the fractions collected was 50 ml. Fractions 1 to 5 (benzene–light petroleum 1 : 1 and 3 : 1) did not contain a weighable residue. From further fractions the following alkaloids were obtained by crystallization from methanol (the weight of the crystalline product, numbers of fractions and elution solvents are given in brackets): tetrahydrocorysamine (23·2 mg; 6—10; benzene), thalictricavine (110 mg; 8—12; benzene), corydaline (230 mg; 10—14; benzene and benzene–ether 10 : 1), stylopine (25·2 mg; 15—16; benzene–ether 4 : 1), canadine (92·8 mg; 16—20; benzene–ether 4 : 1), (+)-tetrahydropalmatine and (±)-tetrahydropalmatine (240 mg and 190 mg, resp.; 19—26; benzene–ether 4 : 1 and 3 : 2), corycavine (150 mg; 27—38; benzene–ether 3 : 2, 1 : 1 and 2 : 3), corycavidine and its mixture with corycavine (60 mg and 70 mg, resp.; 32—40; benzene–ether 1 : 1 and 2 : 3), protopine (10 mg; 39—40, benzene–ether 2 : 3)

and allocryptopine (25·1 mg; 41—51; benzene–ether 2 : 3 and ether). From fractions 6—57 a total of 250 mg of predominantly amorphous bases was obtained, containing in addition to the above-mentioned alkaloids a small amount of bulbocapnine and corydine (fraction 37—39). Fractions 58—60 (chloroform–methanol) contained 0·33 g of orange quaternary protoberberines which were formed on oxidation of corresponding tetrahydroprotoberberines during column chromatography. Fractions 52—57 and 61—65 (50 mg; ether–chloroform 1 : 1, chloroform, chloroform–methanol 1 : 1 and 4 : 1) contained non-alkaloidal substances.

From a solution of bases AC_2 (2·98 g) in chloroform corybulbine (0·18 g) crystallized out while the remaining bases were crystallized from chloroform–ethanol and methanol to afford bulbocapnine (1·09 g), isocorypalmine (48·3 mg) and mixed fractions. From the residue of the bases corydine hydrochloride (base 0·11 g) was obtained on crystallization from dilute hydrochloric acid. Amorphous bases (0·72 g) and dark oxidation products (0·20 g) remained in the filtrate. Bases AD_2 (26·70 g) were crystallized from chloroform–ethanol and methanol to afford bulbocapnine (18·03 g), corypalmine (40 mg), isocorypalmine (8·6 mg) and mixed fractions. From the mother liquors scoulerine (base 28·7 mg) was separated in the form of a poorly soluble hydrochloride.

What remained were 4·72 g of amorphous bases and 0·95 g of decomposition products. From the combined mixed fractions and purified amorphous residues of fractions AC_2 and AD_2 bulbocapnine (0·58 g), corybulbine (0·72 g), corypalmine (0·13 g) and isocorypalmine (41·8mg) were isolated by further crystallizations. The residue of amorphous bases (0·88 g) in 60 ml of benzene was separated on an alumina column (75 g) of the same quality as above. Fractions of 25 ml volume were collected. Fractions 1 to 4 (benzene and benzene–ether 4 : 1) were unweighable, fractions 5 to 17 (benzene–ether 4 : 1 and 1 : 1) contained the residues of non-phenolic bases. From further fractions (the composition of elution solvents is given in brackets) the following alkaloids were obtained by crystallization from methanol: from fraction 18—24 (benzene–ether 1 : 4) bulbocapnine (210 mg), 25—29 bulbocapnine (40 mg), isocorypalmine (5 mg), corypalmine (15 mg), corybulbine (1 mg) and 0·19 g of amorphous bases containing according to TLC corydine and traces of apocavidine, 30—34 (ether), corypalmine (7 mg), scoulerine (16·8 mg) and amorphous bases (90 mg). In this fraction a blue oxidation product of bulbocapnine (1,2-methylenedioxy-6a,7-dehydroaporphine-10,11-quinone)[6] and two further unidentified alkaloids (R_F 0·06 and 0·11 in S_2) were also present. From fractions 30—62 (ether, ether–chloroform 1 : 1, chloroform, chloroform–methanol 1 : 1 and methanol) 0·17 g of amorphous substances were obtained.

From fraction *E* (6·53 g) 0·11 g of corytuberine were separated on crystallization from ethanol. The residue was a mixture of amorphous bases. From fraction *B* 0·87 g (0·073%) of crystalline orange chlorides were obtained in the usual manner, from which 350 mg of dehydrocorydaline chloride, 210 mg of dehydrothalictricavine chloride, 154 mg of corysamine chloride, 9 mg of palmatine chloride, 10 mg of a mixture of the chlorides of palmatine and berberine and 60 mg of mixed fractions (containing in addition to the mentioned alkaloids a small amount of coptisine) were isolated by systematic crystallizations from water.

The picrates of fraction *P* (6·54 g) were converted to chlorides by shaking with 5% hydrochloric acid and ether, excess potassium iodide was added to the aqueous layer, and the mixture extracted several times with chloroform. The crude iodides (186 mg) obtained after distillation of the chloroform afforded 51·3 mg of bulbocapnine methiodide, 19·7 mg of corytuberine hydriodide, 1·8 mg of α-tetrahydrocorysamine methiodide, 1·0 mg of α-stylopine methiodide, 3·5 mg of dehydrocorybulbine iodide and 2·4 mg of the iodide of alkaloid CC2 (needles, m.p. 158—162°C from methanol) on crystallization from methanol. In the mother liquors the presence of magnoflorine (a violet fluorescing spot in UV light, identical with an authentic sample in 3 systems) and dehydroapocavidine was detected by TLC.

Dry ground tubers of sample 2 (130 g) were extracted in the same manner as sample 1 above. Alkaloid fractions *A*, *B* and *E* were isolated from the extract. The remaining aqueous layer was then weakly acidified with dilute sulphuric acid, a potassium iodide solution was added and the mixture extracted several times with chloroform (fraction *I*). The bases of fraction *A* (4·52 g; 3·48%) were separated[24,25] to fractions AC_1, AC_2, AD_1 and AD_2. From the fraction AC_1 (1·47 g) (+)-tetrahydropalmatine (0·60 g) was isolated partly by direct crystallization from ether, and partly in the form of (+)-bitartrate by crystallization from methanol, further (±)-tetrahydropalmatine (0·12 g) by crystallization of the bases from methanol and of the hydrochlorides from water, corydaline (0·13 g), thalictricavine (10 mg) and tetrahydrocorysamine (6·5 mg) by crystallizations from methanol. Canadine (base 35 mg) was separated in the form of poorly soluble hydrochloride by crystallization from methanol. The remainder was 207 mg of amorphous bases. From fraction AC_2 (1·36 g) bulbocapnine (1·07 g), corypalmine (80 mg), corybulbine (15 mg) and isocorypalmine (5 mg) were isolated by crystallizations from ether and methanol. From the residue of bases corydine was isolated (base 90 mg) in the form of poorly soluble hydrochloride. Crystallization of fraction AD_1 (0·29 g) from methanol gave corycavine (0·13 g), protopine (2·4 mg) and capnoidine (5·6 mg), and in the mother liquors small amounts of allocryptopine and corycavidine were detected. Fraction AD_2 (0·85 g) afforded on crystallization from methanol bulbocapnine (0·49 g) while scoulerine (base 45 mg) was obtained from the mother liquors in the form of poorly soluble hydrochloride. Fraction *B* was crystallized from dilute hydrochloric acid to afford 203 mg of orange yellow chlorides (0·156%), from which coptisine chloride (7·1 mg), corysamine chloride (43·6 mg), palmatine chloride (84·0 mg) and berberine chloride (5·1 mg) were obtained on crystallization from water. In the mother liquors trace amounts of dehydrocorydaline were also found in addition to the mentioned alkaloids. Fraction *E* (0·38 g) on crystallization from methanol afforded corytuberine (30·4 mg). Fraction *I* (1·07 g) gave by the same procedure bulbocapnine methiodide (57 mg), corytuberine hydriodide (169 mg) and dehydroapocavidine iodide (14·3 mg). The noncrystallizing residue was separated[18] to the fraction of iodides of nonphenolic bases (I_1) and phenolic ones (I_2). Crystallization of fraction I_1 (36 mg) from methanol gave α-stylopine methiodide (1·0 mg). The main component of the amorphous residue was an unidentified alkaloid (R_F 0·08 in S_6), which would not crystallize either in the form of iodide or perchlorate, and the presence of a small amount of α-tetrahydrocorysamine methiodide and alkaloid CC2 was also detected. In fraction I_2 (143·4 mg) dehydrocorybulbine, dehydroapocavidine, jatrorrhizine, columbamine, magnoflorine and other unidentified alkaloids were detected by TLC in the systems S_6, S_7 and S_8. A part of fraction I_2 (72 mg) was reduced with sodium borohydride, the solution was acidified with dilute sulfuric acid, then alkalized with ammonia and extracted with ether. The residue (10·7 mg) was crystallized from methanol to give 1·4 mg of needles of m.p. 203—205°C, undepressed in admixture with authentic (±)-corybulbine. In the mother liquors apocavidine, corypalmine and isocorypalmine were detected in addition to the residue of corybulbine.

Alkaloids from the Aerial Parts

Dry ground aerial parts (sample 1: 388 g; sample 2: 57 g) were extracted in the same manner as described above. From the extract alkaloidal fractions *A*, *B*, *I* and *E* were obtained. In the following text the yields are given in brackets for sample 1 and 2, respectively.

From fraction *A* (1·65 g; 0·44 g) bulbocapnine (226 mg; 137 mg; total yield: 565 mg, 0·15%; 172 mg, 0·30%) was isolated by crystallization from methanol and the rest of the bases was separated to a non-phenolic fraction A_1 and a phenolic one, A_2. From fraction A_1 protopine (33 mg, 0·009%, 2·3 mg, 0·004%), (+)-stylopine (6·2 mg; 0·0016%; 21·5 mg, 0·038%), capnoidine (9·4 mg, 0·0024%; 17·0 mg, 0·030%) and alkaloid CCl (1·1 mg; 1·1 mg) were obtained by crystal-

lization from ether. The remaining amorphous bases of sample 1 afforded on crystallization from dilute hydrochloric acid a mixture of hydrochlorides of approximately equal amounts of glaucine and domestine (bases 61 mg, 0·016%) which were partly separated by crystallization of the hydrochlorides and identified by TLC. In the amorphous residue of the bases (102 mg; 60 mg) several additional unidentified alkaloids were detected by TLC. Fraction A_2 when crystallized from ether gave bulbocapnine (339 mg; 35 mg). In the amorphous residue (158 mg; 40 mg) predicentrine, corydine and isoboldine were detected as the main components by TLC, in addition to smaller amounts of several additional unidentified alkaloids. Fraction *B* was converted to chlorides (0·12 g, 0·031%; 40 mg, 0·070%) and crystallized from water to give coptisine chloride (87 mg, 0·022%; 29 mg, 0·051%), while from the mother liquors corysamine chloride (8·5 mg, 0·002%; in sample 2 it was detected by TLC) was obtained. In fraction *I*, which was predominantly non-alkaloidal, trace amounts of bulbocapnine methiodide were detected by TLC. Fraction *E* was practically non-alkaloidal.

Characterization of the Isolated Alkaloids

The alkaloids in *C. cava* which were described earlier were also identified by IR and UV spectra in addition to the mentioned physical constants, by comparing them with the data of authentic samples or with the published data[26] and R_F values. Unless stated otherwise the yields in % of the dry tubers of sample 1 and sample 2 are given in brackets.

(+)-*Bulbocapnine* (1·67%; 1·20%): prisms m.p. 201–202°C (chloroform–ethanol), $[\alpha]_D^{22}$ +237° ±2° (*c* 0·50, chloroform). Hydrochloride m.p. 260–265°C (methanol). Methiodide: bulbocapnine (102 mg) was dissolved in 1 ml of chloroform, 2 ml of methanol and 1 ml of methyl iodide were added and the mixture allowed to stand for 24 h. The product (143 mg) crystallized out, m.p. 267–268°C (methanol), $[\alpha]_D^{22}$ +162° ± 3° (*c* 0·24, methanol).

(+)-*Corydaline* (0·57%; 0·10%): prisms m.p. 134–135°C (methanol), assuming a yellow colour in air, $[\alpha]_D^{22}$ +313° ± 3° (*c* 0·50, methanol), +302° ± 3° (*c* 0·50, chloroform). Mass spectrum: ions of *m/e* 369 (M^+), 192, 190, 178, 163, 135. Hydrochloride m.p. (unsharp) 208°C (water), poorly soluble in water.

(+)-*Tetrahydropalmatine* (0·23%; 0·46%): from ethanol–water plates of m.p. 115–116°C (hydrate), from ether needles of m.p. 142–143°C, undepressed on admixture with an authentic sample*, turning yellow in air, $[\alpha]_D^{22}$ +292° ± 3° (*c* 0·29, methanol).

(±)-*Tetrahydropalmatine* (0·078%; 0·092%): plates of m.p. 148–149°C (ethanol), undepressed on admixture with a preparation prepared from palmatine*, $[\alpha]_D^{22}$ 0° ± 3° (*c* 0·12, methanol).

Corycavine (0·204%; 0·10%): prisms m.p. 218–219°C (chloroform–methanol), $[\alpha]_D^{22}$ 0° ± 3° (*c* 0·37, chloroform). IR spectrum: ν(CO) 1 645 cm^{-1}. Hydrochloride m.p. 225–232°C (water), poorly soluble in water.

Thalictricavine (0·084%; 0·008%): when the crude preparation of the sample 1 was crystallized several times from chloroform–methanol (±)-thalictricavine (60 mg; 0·005%) was obtained as the least soluble fraction, m.p. 202–204°C (literature[28]: m.p. 204°C), $[\alpha]_D^{22}$ 0° ± 3° (*c* 0·37,

* A sample for comparison was prepared from palmatine chloride (m.p. 205–210°C) isolated from the roots of *Jatrorrhiza palmata* MIERS. by reduction to (±)-tetrahydro derivative, m.p. 148–149°C (ethanol). Crystallizations of (+)-bitartrate according to ref.[27] of this preparation gave (+)-tetrahydropalmatine, m.p. 140–141°C (benzene–light petroleum), $[\alpha]_D^{22}$ +291° ± ± 3° (*c* 0·34, (ethanol)).

chloroform), IR spectrum (Bohlmann's bands in the 2700—2800 cm^{-1} region) identical with the spectrum of the (+)-form and the data from literature[26]. From the better soluble fractions 0·89 g (0·075%) of pure (+)-thalictricavine, prisms m.p. 147—148°C, turning yellow in air, $[\alpha]_D^{23}$ +286° ± 3° (*c* 0·34, chloroform). Mass spectrum: ions of *m/e* 353 (M^+), 178, 174, 163 and 135.

(+)-*Corybulbine* (0·076%; 0·012%): prisms m.p. 226—228°C (chloroform–methanol), $[\alpha]_D^{22}$ +308° ± 3° (*c* 0·19, chloroform).

Protopine (0·028%; 0·002%): prisms m.p. 206—207°C (chloroform–methanol), undepressed on admixture with an authentic sample.

Corycavidine (0·019%; traces): (+)-form, prisms, m.p. 213—214°C (methanol), $[\alpha]_D^{25}$ +200° ± 3° (*c* 0·24, chloroform). IR spectrum: ν(CO) 1 640 cm^{-1}. UV spectrum: λ_{max} (log ε) 210 nm (4·78), 288 nm (3·88), shoulder 230 nm (4·15), λ_{min} 262 nm (3·58). From the mother liquors after crystallization of the (+)-form (±)-corycavidine (37 mg; 0·003%), prisms, m.p. 192—193°C (methanol) was isolated, $[\alpha]_D^{25}$ 0° ± 3° (*c* 0·15, chloroform).

(+)-*Corypalmine* (0·015%; 0·062%): needles, m.p. 223—224°C (chloroform–methanol), $[\alpha]_D^{22}$ +301° ± 3° (*c* 0·18, chloroform). IR and UV spectra were identical with the spectra of (±)-corypalmine (tetrahydrojatrorrhizine) prepared on reduction of jatrorrhizine isolated from the roots of *Berberis vulgaris* L.

(+)-*Corytuberine* (0·011%; 0·11%): needles, m.p. 241—242°C (methanol), $[\alpha]_D^{24}$ +288° ± 5° (*c* 0·10, methanol). Hydriodide, plates, m.p. 210—212°C (methanol) (*cf.*[13]).

(+)-*Corydine* (0·009%; 0·069%): needles, m.p. 148—149°C (ether), undepressed with an authentic specimen, $[\alpha]_D^{23}$ +204° ± 3° (*c* 0·11, methanol).

Isocorypalmine (0·009%; 0·004%): crystallization of the crude preparation from sample 1 gave (±)-isocorypalmine (80 mg; 0·007%), prisms, m.p. 215—216°C (chloroform–methanol), undepressed on admixture with a preparation obtained on reduction of columbamine[29], $[\alpha]_D^{22}$ 0° ± 3° (*c* 0·19, chloroform). From the mother liquors 23 mg (0·002%) of a more soluble product were obtained, m.p. 220—222°C (methanol), which according to its rotation value $[\alpha]_D^{24}$ +108° ± 3° (*c* 0·13, chloroform) was a mixture of the (+)- and the (±)-form.

(+)-*Canadine* (0·008%; 0·027%): needles m.p. 131—132°C (methanol), $[\alpha]_D^{24}$ +288° ± 3° (*c* 0·21, methanol). The IR and UV spectra were identical with those of (±)-canadine prepared on reduction of berberine. Hydrochloride, m.p. 218°C (methanol).

(+)-*Stylopine* (0·007%; traces): needles m.p. 201—202°C (chloroform–methanol), $[\alpha]_D^{23}$ +309° ± 3° (*c* 0·22, chloroform).

(−)-*Scoulerine* (0·004%; 0·035%): needles m.p. 201—202°C (ether), undepressed on admixture with and authentic sample, turning red in air, $[\alpha]_D^{24}$ −354° ± 10° (*c* 0·08, methanol). Hydrochloride, m.p. 248—258°C (methanol), mixture melting point identical.

Allocryptopine (0·002%; traces): prisms m.p. 160—161°C (methanol), undepressed on admixture with an authentic specimen.

(+)-*Tetrahydrocorysamine* (0·002%; 0·005%): from methanol, needles m.p. 134—135°C or compact spherical clusters, m.p. 178—180°C, $[\alpha]_D^{23}$ +235° ± 3°(*c* 0·09, methanol). Literature[8,9] gives m.p. 136—137°C or 180—181°C, and $[\alpha]_D$ −233° or +236° (in chloroform), for the (−)- or the (+)-form respectively. IR spectrum (Bohlmann's bands in the 2700—2800 cm^{-1} region) and UV spectrum, λ_{max} (log ε) 208 nm (4·67), 290 nm (3·91), shoulder 236 nm (3·90), λ_{min} 258 nm (2·82), were identical with the spectra of (±)-tetrahydrocorysamine prepared on re-

duction of corysamine[10]. Methiodide: 3·0 mg of (+)-tetrahydrocorysamine were refluxed with 3 ml of acetone and 0·5 ml of methyl iodide for 8 h on a water bath. Crystallization of the product from methanol afforded a mixture of α- and β-methiodide, m.p. unsharp 230—250°C, and pure (+)-β-methiodide (according to paper chromatography in S_{11}, see below) m.p. 244—246°C.

Capnoidine (—; 0·004%): prisms m.p. 235—237°C (chloroform–methanol), undepressed on admixture with an authentic sample, $[\alpha]_D^{24}$ —116° ± 5° (*c* 0·12, chloroform). IR spectrum, ν(CO) 1750 cm^{-1}, and UV spectrum identical with the literature data[26].

Alkaloid CCl (probably dehydrodomestine; aerial part: 0·0003%; 0·002%): needles m.p. 194 to 196°C (methanol). Mass spectrum: M^+ 377, 1301, for $C_{20}H_{19}NO_4$ calculated 337·1314.

Dehydrocorydaline chloride (0·029%; traces): orange yellow needles from water, m.p. 170 to 180°C (decomp.), mixture melting point with a preparation obtained from corydaline undepressed. IR and UV spectra and R_F values were identical with those of a standard.

Dehydrothalictricavine chloride (0·018%; —): from water, yellow needles, m.p. 185—195°C (decomp.), undepressed on admixture with a preparation prepared from thalictricavine. IR and UV spectra and R_F values were identical with those of a standard.

Corysamine chloride (0·013%; 0·034%): from water, bronze coloured leaves, not melting up to 300°C (blackening, decomposition); an authentic sample[10] behaved in the same manner. Their identity was also confirmed by IR and UV spectra and R_F values.

Palmatine chloride (0·001%, 0·065%): orange-yellow needles from water, m.p. 203—207°C, undepressed in admixture with a preparation from *Jatrorrhiza palmata*. The identity was also confirmed by IR and UV spectra and R_F values.

Coptisine chloride (traces; 0·005%): from water orange needles, not melting up to 350°C (decomposition and blackening); an authentic sample behaved in the same manner. The identity was proved by IR and UV spectra and R_F values.

Berberine chloride (isolated in a mixture; 0·004%): yellow needles m.p. 200 – 208°C, undepressed on admixture with an authentic sample[10] (m.p. 208—210°C). The identity was also confirmed by R_F values.

Dehydrocorybulbine iodide (0·0003%; after reduction 0·002% of tetrahydro derivative): yellow needles m.p. 205—215°C (methanol), undepressed with a preparation from corybulbine. The identity was confirmed by R_F values and reduction with sodium borohydride to (±)-corybulbine, m.p. 206—208°C (methanol), undepressed in admixture with a sample prepared on reduction of authentic dehydrocorybulbine; R_F values also coincided.

Dehydroapocavidine iodide (traces; 0·011%): from methanol orange-yellow clusters, m.p. 300—308°C (decomp.). UV spectrum: λ_{max} (log ε) 222 nm (4·55), 268 nm (4·45), 349 nm (4·36), λ_{min} 250 nm (4·35) and 308 nm (3·76). On reduction with sodium borohydride (±)-apocavidine was obtained, colourless needles of m.p. 166—168°C from methanol[12].

Bulbocapnine methiodide (0·0043%, 0·044%): needles of m.p. 268—269°C (methanol), undepressed on admixture of a sample prepared from bulbocapnine, $[\alpha]_D^{22}$ +163° ± 3° (*c* 0·11, methanol). Mass spectrum: at ion source temperature the sample was pyrolysed to methine, M^+ 339·1496 (for $C_{20}H_{21}NO_4$ calculated 339·1470) and a tertiary base, M^+ 325·1308 (for $C_{19}H_{19}NO_4$ calculated 325·1314); the spectrum also contained peaks of methyl iodide and iodine (*m/e* 142 and 127). The IR spectrum, ν(OH) 3370 cm^{-1}, and UV spectrum, λ_{max} (log ε) 225 nm (4·75), 272 nm (4·25), 310 nm (4·02), λ_{min} 256 nm (3·97) and 291 nm (3·85), were identical with the spectra of a standard. The same is true of the R_F values.

α-*Tetrahydrocorysamine methiodide* (0·0002%; detected by TLC): needles of m.p. 285—293°C (methanol). Mass spectrum: ions of *m/e* 337 ($M-CH_3I$), 176, 174, 162 (base peak), 142 (CH_3I), 127 (I). The preparation was contaminated with a small amount of stylopine methiodide (peaks *m/e* 323 and 148), detectable by TLC. The R_F values in five systems were identical with the values of an authentic sample of (±)-α-tetrahydrocorysamine methiodide prepared from (±)-tetrahydrocorysamine.

(+)-α-*Stylopine methiodide* (0·0001%; 0·0008%): needles m.p. 275—276°C (methanol), undepressed on admixture with an authentic specimen. The identity was confirmed by R_F values and a characteristic colour reaction with Erdmann's reagent (blue-green to blue).

Preparation of Quaternary Protoberberines

Quaternary protoberberines were prepared from corresponding tertiary tetrahydroprotoberberine alkaloids by oxidation with mercuric acetate, using a procedure described in ref.[29]. From the reaction mixture dehydrocorybulbine iodide was obtained by the procedure described in the paper mentioned, while in the case of non-phenolic protoberberines the solution was alkalized with sodium hydroxide, extracted with ether and the base obtained was converted to its chloride by crystallization from dilute hydrochloric acid (1 : 10).

Dehydrocorydaline chloride: orange yellow needles, m.p. 170—180°C (decomp.). UV spectrum: λ_{max} (log ε) 231 nm (4·30), 266 nm (4·41), 336 nm (4·32), λ_{min} 248 nm (4·21), 305 nm (3·91). On reduction with sodium borohydride and crystallization from methanol (±)-corydaline was obtained, prisms, m.p. 134—135°C, and (±)-mesocorydaline, needles of m.p. 157—159°C.

Dehydrothalictricavine chloride: yellow needles, m.p. 185—197°C (decomp.). UV spectrum: λ_{max} (log ε) 232 nm (4·43), 266 nm (4·46), 342 nm (4·36), λ_{min} 250 nm (4·26), 305 nm (3·93).

Palmatine chloride: orange-yellow needles, m.p. 205—210°C (decomp.) UV spectrum: λ_{max} (log ε) 230 nm (4·48), 268 nm (4·39), 342 nm (4·38), λ_{min} 254 nm (4·28), 307 nm (3·92).

Dehydrocorybulbine iodide: yellow needles, m.p. 210—220°C (decomp.). UV spectrum: λ_{max} (log ε) 222 nm (4·53), 266 nm (4·40), 340 nm (4·28), λ_{min} 249 nm (4·28), 308 nm (3·93). Reduction with sodium borohydride gave (±)-corybulbine, m.p. 208—211°C (methanol).

Preparation of (±)-α- and β-Tetrahydrocorysamine Methiodides

Corysamine chloride (200 mg) isolated from *Chelidonium majus*[10] was reduced with zinc in dilute sulfuric acid for about one hour, then filtered, alkalized with ammonia and extracted with ether. When crystallized from chloroform–methanol the residue afforded (±)-tetrahydrocorysamine (56·8 mg), needles of m.p. 203—204°C (methanol). From the mother liquors (±)-mesotetrahydrocorysamine (62·1 mg) was obtained, needles after crystallization from ether, m.p. 134—136°C (literature[30]: m.p. 137—138°C), R_F 0·67 (S_1). (±)-Tetrahydrocorysamine (20·7 mg) was dissolved in 5 ml of acetone, 1 ml of methyl iodide was added and the mixture refluxed for 6 h (according to ref.[19]). Crystallization of the product from methanol gave 5·3 mg of the starting base, 9·3 mg (±)-α-tetrahydrocorysamine methiodide, clusters with m.p. 266—268°C (literature[19]: m.p. 266°C), R_F 0·77 (S_{11}), and 7·8 mg (±)-β-tetrahydrocorysamine methiodide, needles of m.p. 238—240°C, R_F 0·58 (S_{11}). In thin-layer chromatography (in S_6, S_7 and S_8) the α-form had the same R_F values as the β-form. UV spectrum of (±)-α-tetrahydrocorysamine methiodide: λ_{max} (log ε) 210 nm (4·84), 292 nm (4·32), shoulder 250 nm (3·88), λ_{min} 262 nm (3·19).

R_F Values

In system S_1, S_2, S_3, S_4 and S_5, respectively: alkaloid CCl 0·46, 0·81, —, 0·60, 0·69; allocryptopine 0·26, 0·76, —, 0·20, 0·26; apocavidine 0·15, 0·39, 0·62, 0·85, 0·90; bulbocapnine 0·17, 0·51, 0·69, 0·64, 0·75; canadine 0·62, 0·89, —, 0·88, 0·90; capnoidine 0·14, 0·61, —, 0·87, 0·86; corybulbine 0·14, 0·35, 0·57, 0·87, 0·87; corycavidine 0·32, 0·84, —, 0·37, 0·54; corycavine 0·43, 0·82, —, 0·51, 0·76; corydaline 0·56, 0·91, —, 0·86, 0·90; corydine 0·18, 0·54, 0·72, 0·55, 0·71; corypalmine 0·09, 0·26, 0·45, 0·87, 0·91; domestine 0·42, 0·77, —, 0·63, 0·70; glaucine 0·28, 0·78, —, 0·54, 0·64; isoboldine 0·02, 0·05, 0·11, 0·55, 0·71; isocorypalmine 0·11, 0·32, 0·52, 0·84, 0·87; 1,2-methylenedioxy- 6a,7-dehydroaporphine-10,11-quinone —, 0·36, 0·61, 0·80, 0·82; predicentrine 0·03, 0·09, 0·31, 0·59, 0·71; protopine 0·38, 0·79, —, 0·26, 0·45; scoulerine 0·04, 0·15, 0·38, 0·84, 0·88; stylopine 0·71, 0·89, —, 0·87, 0·88; tetrahydrocorysamine 0·81, 0·93, —, 0·89, 0·91; tetrahydropalmatine 0·42, 0·87, —, 0·82, 0·84; thalictricavine 0·76, 0·92, —, 0·86, 0·91. In system S_6, S_7, S_8, S_9 and S_{10}, respectively: alkaloid CC2, 0·54, 0·23, 0·78, —, —; berberine —, —, —, 0·26, 0·79; bulbocapnine methiodide 0·20, 0·09, 0·70, 0·02, 0·01; columbamine 0·59, 0·43, 0·79, 0·40, 0·32; coptisine —, —, —, 0·62, 0·93; corysamine 0·40, 0·16, 0·80, 0·14, 0·73; corytuberine 0·86, 0·88, 0·77, —, —; dehydroapocavidine 0·52, 0·37, 0·75, 0·29, 0·26; dehydrocorybulbine 0·79, 0·63, 0·82, 0·52, 0·30; dehydrocorydaline —, —, —, 0·17, 0·22; dehydrothalictricavine —, —, —, 0·20, 0·35; jatrorrhizine 0·73, 0·60, 0·81, 0·51, 0·40; magnoflorine 0·58, 0·42, 0·64, 0·05, 0·02; palmatine —, —, —, 0·19, 0·65; α-stylopine methiodide 0·44, 0·18, 0·82, —, —; α-tetrahydrocorysamine methiodide 0·52, 0·21, 0·87, —, —. In system S_{11} and S_{12}, respectively: berberine 0·61, 0·18; coptisine 0·45, 0·09; corysamine 0·73, 0·53; dehydrocorydaline 0·77, 0·76; dehydrothalictricavine 0·82, 0·72; palmatine 0·57, 0·33; α-stylopine methiodide 0·66, —; α-tetrahydrocorysamine methiodide 0·77, —.

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Note added in proof: Quite recently Prof. N. Takao, Kobe, Japan (private communication) prepared (±)-α-tetrahydrocorysamine methiodide (m.p. 267—269°C) and (±)-β-tetrahydrocorysamine methiodide (m.p. 239—241°C). Direct comparison with our samples proved mutual identity. We thank Prof. Takao for his kind donation of his preparations.