MINOR ALKALOIDS FROM *Chelidonium majus* L.*

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From the fraction of quaternary alkaloids, obtained from the roots or the overground parts of *Chelidonium majus* L., magnoflorine or (−)-α-stylopine methohydroxide and (−)-β-stylopine methohydroxide, respectively, were isolated in the form of iodides. The weakly basic non-quaternary fraction from the root yielded dihydrosanguinarine, dihydrochelerythrine and the new alkaloid dihydrochelirubine in addition to oxysanguinarine. Further a small amount of dihydrochelilutine and N-demethyl-9,10-dihydrooxysanguinarine (compound X) was also detected.

Chelidonium majus L. – a medicinal plant employed from time immemorial – is one of the most often investigated plants of the *Papaveraceae* family, owing to its chemically and pharmacologically interesting alkaloids[1]. Among the new alkaloids from the roots chelamine $C_{20}H_{19}NO_6$ and chelamidine $C_{21}H_{23}NO_6$ have been described recently[2], to which according to spectral analyses the structure of 10-hydroxychelidonine (*Ia*) and 10-hydroxyhomochelidonine[3] (*Ib*) belongs; more recently the alkaloid chelidimerine (the *meso*-form of 1,3-bis-(1-hydrosanguinarinyl)acetone)[4,5] has also been isolated. Although recently a larger number of authors[2,4,6–13] have investigated the alkaloids from *Ch. majus*, no attention has been given to the question of the presence of those quaternary alkaloids which in contrast to quaternary benzophenanthridines and protoberberines cannot be extracted with non-polar solvents from alkaline medium. In order to solve this question we worked up preliminarily a small amount of the plant material only. As it is known that the root and the aerial part of the plant differ substantially both in the content and in the composition of their alkaloids[1,2,7–14], we investigated both these parts separately. In both cases the procedure was the same: first the acidified aqueous extract was extracted with ether in order to separate non-basic or very weakly basic substances (fraction *L*), then the aqueous solution was weakly alkalinized and extracted again with ether to give fraction *A*, and finally strongly alkalinized and extracted with ether to give fraction *B*. The remaining quaternary alkaloids were obtained after their conversion to iodides by extraction with chloroform, using the procedure applied currently in our

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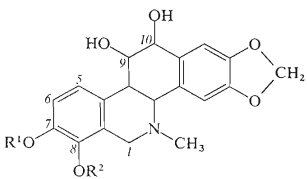
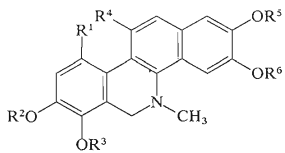
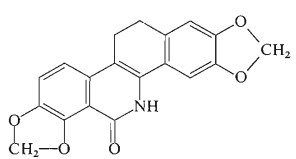
investigations[15,16]. The quaternary fraction from the root afforded magnoflorine iodide as the main alkaloid in a relatively high yield (0·19%), while the aerial part contained a substantially lower amount of quaternary alkaloids. From this material (−)-α-stylopine methiodide (0·005%) and (−)-β-stylopine methiodide (0·003%) were isolated. Both these alkaloids were also detected in trace amounts in the root.



Ia, $R^1 + R^2 = CH_2$
Ib, $R^1 = R^2 = CH_3$



IIa, $R^1 = R^4 = H$, $R^2 + R^3 = R^5 + R^6 = CH_2$
IIb, $R^1 = R^4 = H$, $R^2 = R^3 = CH_3$, $R^5 + R^6 = CH_2$
IIc, $R^1 + R^4 = H + OCH_3$, $R^2 + R^3 = R^5 + R^6 = CH_2$
IId, $R^1 + R^4 = H + OCH_3$, $R^2 = R^3 = CH_3$, $R^5 + R^6 = CH_2$
IIe, $R^1 + R^4 = H + OCH_3$, $R^2 = R^3 = R^5 = R^6 = CH_3$



III

SCHEME 1

The non-basic or weakly basic alkaloid fraction was studied only sporadically so far[1]. From this fraction (*L*) from the root we obtained in addition to oxysanguinarine, which was isolated earlier[1], dihydrosanguinarine (*IIa*), dihydrochelerythrine (*IIb*) and dihydrochelirubine (*IIc*), and we also ascertained the presence of smaller amounts of dihydrochelilutine (*IId*). In the aerial part we detected only trace amounts of dihydrosanguinarine and dihydrochelerythrine. The finding of dihydrochelirubine and dihydrochelilutine in *Ch. majus* represents so far the first occurrence of these two substances in nature. The identity of all the dihydrobenzophenanthridines mentioned was proved by direct comparison with authentic samples (dihydrochelilutine had not been described in the literature up to that date) and by their oxidation to corresponding quaternary alkaloids which also occur in *Ch. majus* naturally[17]. The presence of dihydrosanguilutine (*IIe*) which was recently isolated from the roots of *Sanguinaria canadensis* L.[18] was not detected in *Ch. majus*.

In addition to the compounds mentioned a small amount of substance X isolated[1] earlier from the roots of *Ch. majus* (0·006%) was found in fraction *L* from the roots. The composition $C_{21}H_{15}NO_6$, proposed earlier[1], should be corrected to $C_{19}H_{13}.NO_5$, which was determined by mass spectrometry. The IR spectrum in chloroform displays bands at 815 and 840 cm^{-1} (1,2,3,4-tetrasubstituted aromatic ring), 865 and 880 cm^{-1} (1,2,4,5-tetrasubstituted aromatic ring), 940 cm^{-1} (O_2CH_2), 1040 and 1060 cm^{-1} (C—O—C bonds), 1485, 1505 and 1595 cm^{-1} (aromatic ring), 1650 cm^{-1} (amide CO group), 2890 cm^{-1} (CH-stretching) and 3100 cm^{-1} (amide NH group). In its mass spectrum characteristic peaks appeared at *m/e* 335 (M^+), 320 (M − 15) and 292 (M − 43). In the ^{1}H-NMR spectrum (in $CDCl_3$) two triplets are present at 2·81 ppm, J = 6 Hz, and at 4·21 ppm, J = 6 Hz (AA'BB' system, protons —CH_2—CH_2—), further two two-proton singlets at 5·93 and 6·13 ppm ($2\,O_2CH_2$), a doublet at 7·07 and 6·95 ppm, J = 8 Hz (AB system, two aromatic *ortho*-protons), a singlet at 7·17 ppm (one aromatic proton) and a broad band at 7·38 ppm (one proton?). These results are in agreement with the assumed structure of N-demethyl-9,10-dihydrooxysanguinarine (*III*).

The alkaloids from fraction *A* of the roots, which we studied in detail in preceding papers[1,2], were not further investigated. However, we again paid attention to this alkaloidal fraction from the aerial parts, which has been studied in our country only once[14], and that at a different vegetation period. While in the material used in paper[14] (collection at the period of ripe seeds) chelidonine was the main alkaloid, we now isolated coptisine as the main alkaloid from the aerial parts of the plant collected at the beginning of the flowering period, further (±)-stylopine and (−)-stylopine (in an approximately 10 : 1 ratio), further a smaller amount of chelidonine and protopine, and minute amounts of allocryptopine, sanguinarine, berberine and corysamine. From comparison with the results from paper[14] as well as other papers[7–13] it is evident that the occurrence and the relative amounts of individual alkaloids are considerably dependent both on geographic and climatic conditions,

and on the vegetation stage of the plant. In contrast to paper[4] we were unable to prove even traces of chelidimerine in our plant material.

EXPERIMENTAL

The melting points were determined on a Kofler block (unless stated otherwise), and they were not corrected. The mass spectra were measured on an AEI-MS 902 spectrometer, the ^{1}H-NMR spectrum was measured in deuteriochloroform on a Varian HA-100 instrument (using hexamethyldisiloxane as internal reference, $\delta = 0{\cdot}05$ ppm), the IR spectra on a Zeiss UR 10 and the UV spectra (in methanol) on a Unicam SP 1800 spectrophotometer. For thin layer chromatography both Silicagel G (Merck) with gypsum (5 : 1) and the solvent systems cyclohexane–diethylamine 9 : 1 (S_1), cyclohexane–chloroform–diethylamine 7 : 2 : 1 (S_2), benzene (S_3), benzene–diethylamine 19 : 1 (S_4), benzene–methanol 18 : 1 (S_5) and 4 : 1 (S_6), ethanol–water–25% ammonia 15 : 9 : 1 (S_7), methanol–water–25% ammonia 15 : 3 : 1 (S_8) and 1-propanol–water–85% formic acid 12 : 7 : 1 (S_9), and Silufol UV 254 (Kavalier) with the system cyclohexane saturated with methanol (S_{10}), methanol saturated with cyclohexane (S_{11}) and methanol–diethylamine 4 : 1 (S_{12}) were used. Paper chromatography was carried out in ascending manner on paper Whatman No 1 in the system 1-butanol–acetic acid–water 10 : 1 : 3 (S_{13}) and ethanol–water 3 : 2 (S_{14}). The spots of fluorescing alkaloids were detected under the UV light, and the spots of other alkaloids with potassium iodoplatinate (on thin layers) or Dragendorff's reagent (on paper).

Extraction and Isolation of Alkaloids

The plants were collected at a natural locality in Brno (roots on September 8, 1975, aerial parts on May 20, 1976) and dried at room temperature. The ground plant material (200 g of roots and 947 g of the aerial parts) was extracted in a Soxhlet extractor. Ethanol from the extract was distilled off and the residue transferred into 1% sulfuric acid and filtered. The acid aqueous filtrate was first extracted several times with larger portions of ether (fraction *L*), and the alkaloid fractions *A*, *B*, *I* and *E* were then obtained from the aqueous layer in the usual manner[15,19].

Alkaloids from Roots

The ethereal solution of fraction *L* was first extracted with 2% sulfuric acid in order to separate basic substances (present in trace amounts only), and then with a dilute ammonia solution, in order to eliminate substances of acid character, which were not further investigated. Ether was distilled off. The residue was crystallized from chloroform–methanol yielding 90 mg of dihydrosanguinarine (0·045%) and 10 mg of oxysanguinarine (0·005%), needles m.p. 350–353°C (chloroform–methanol), R_F values 0·08 (S_1), 0·42 (S_2), 0·62 (S_4), 0·59 (S_5) and 0·76 (S_6) were identical with those of an authentic specimen (violet fluorescence). Systematic crystallization of the remaining substances from methanol gave 15 mg of dihydrochelerythrine (0·008%) and 14 mg of dihydrochelirubine (0·007%) which according to thin-layer chromatography contained traces of dihydrosanguinarine. The partly crystalline residue of the mother liquors (30 mg) contained dihydrochelilutine as the main component in addition to the residues of the three mentioned dihydro derivatives and a small amount of compound X. Dihydrochelilutine gave a violet fluorescencing spot, with R_F values in S_1, S_2, S_3 and S_{10} identical with those of an authentic specimen; in air it turned yellow-orange; and on oxidation it gave a product with flesh-coloured fluorescence and R_F values in S_{11}, S_{13} and S_{14} identical with those of authentic chelilutine.

The presence of chelidimerine (authentic sample[4,5] had R_F 0·20 in S_1, 0·56 in S_2, 0·36 in S_3 and 0·16 in S_{10}) could not be detected.

Bases of fraction *A* (3·85 g; 1·93%) were not further investigated. From fraction *B* crystallization from dilute hydrochloric acid gave 0·50 g of coptisine chloride, admixed with a small amount of berberine chloride. From the mother liquors which were alkalized with sodium hydroxide and extracted with ether 0·03 g of bases were obtained which according to chromatography in S_{12}, S_{13} and S_{14}, respectively, contained berberine (R_F 0·18, 0·57 and 0·16, resp.) and corysamine (R_F 0·11, 0·68 and 0·50, resp.) in addition to coptisine (R_F 0·47, 0·47 and 0·07, resp.). The total yield of the quaternary protoberberines, referred to coptisine base, was 0·25%. The purified fraction *I* (0·63 g) was crystallized from methanol to afford 0·38 g of magnoflorine iodide (0·19%). The amorphous residue after fraction *I* was separated (see[16]) to iodides of non-phenolic (I_1) and phenolic (I_2) quaternary alkaloids. From fraction I_1 (14 mg) 1·0 mg of an iodide was obtained by crystallization from methanol, melting at 280—290°C, which was identified as α-stylopine methiodide with an admixture of β-stylopine methiodide by chromatography in S_7, S_8, S_9 and S_{13}. From the mother liquors a crystalline fraction (2·0 mg) was obtained which was a mixture of α- and β-stylopine methiodide and a second alkaloid of R_F values 0·39 in S_7, 0·37 in S_8 and 0·73 in S_9. Fraction I_2 (52 mg) remained amorphous, and according to thin-layer chromatography it contained a single alkaloid, remains of magnoflorine. Fraction *E* was amorphous (0·02 g).

Alkaloids from the Aerial Parts

The ethereal solution of fraction *L* was extracted with a 4% sodium hydroxide solution in order to separate acidic substances, and ether was then distilled off. Crystallization of the residue from chloroform–methanol gave 60 mg of (±)-stylopine. In the amorphous residue (135 mg) traces of dihydrosanguinarine and dihydrochelerythrine could be detected by thin-layer chromatography.

Crystallization of the bases of fraction *A* (yield 1·31 g; 0·14%) from chloroform–methanol gave 0·51 g of stylopine (total yield 0·61 g; 0·065%), from which 0·40 g of pure (±)-stylopine could be isolated by further crystallization from chloroform–methanol. Total yield 0·47 g (0·050%) needles of m.p. 221—222°C, undepressed on admixture with an authentic specimen. From the mother liquors 0·02 g of (−)-stylopine were obtained, total yield 0·05 g (0·005%), needles from chloroform–methanol, m.p. 198—200°C, undepressed in admixture with an authentic sample (m.p. 201—202°C). According to its specific rotation, $[\alpha]_D^{26}$ −251° ± 3° (*c* 0·15, chloroform) this preparation was contaminated with about 20% of racemate (for the pure (−)-form the value $[\alpha]_D^{23}$ −314° ± 3°, in chloroform, was found[20]). The R_F value and the colour reactions were identical as in the case of (±)-stylopine. After crystallization of stylopine chelidonine hydrochloride crystallized out from the mother liquors after acidification with conc. hydrochloric acid. Chelidonine base (0·24 g; total yield 0·33 g; 0·035%) formed prisms of m.p. 135—136°C (ether), undepressed in the presence of an authentic sample with which it also had identical R_F value, 0·33 in S_1, and colour reactions. The remaining alkaloids were then separated to two hydrochloride fractions: extractable with chloroform (*AC*) and unextractable (*AD*). From the bases of fraction *AC* 0·01 g of (±)-stylopine and 0·03 g of (−)-stylopine were obtained by crystallization from ether. After this 0·04 g of amorphous bases remained. From the bases of fraction *AD* non-basic pseudocyanides were separated first in the usual manner[14,17]. The base (3·7 mg; 0·0004%) prepared from them was identified as chromatographically pure sanguinarine. The remaining bases of fraction *AD* were crystallized from ether and methanol to afford 0·28 g of protopine (0·030%), prisms of m.p. 203—204°C (chloroform–methanol), undepressed on admixture of an authentic sample. Their R_F value (0·43 in S_1) and colour reactions were also identical. From the mother liquors a further fraction of chelidonine was isolated in the form of hydrochlo-

ride (0·09 g of base), while crystallization of the remainder of the bases from methanol gave 4·4 mg of allocryptopine, m.p. 153—154°C (methanol), undepressed in admixture with an authentic specimen; R_F value, 0·27 in S_1, and colour reactions were also identical. The remaining amorphous residue weighed 0·04 g.

Crystallization of fraction *B* from dilute hydrochloric acid gave 0·86 g of chromatographically pure coptisine chloride (0·82 g of base; 0·087%), and from the mother liquors 0·14 g of bases were obtained in the above mentioned manner, which represented a mixture of coptisine and a small amount of berberine and corysamine. The total yield of quaternary protoberberines was 0·10%. Crystallizations of fraction *I* from methanol gave 26·1 mg of poorly soluble (—)-β-stylopine methiodide (0·028%); from the mother liquors 51·4 mg of the better soluble (—)-α-stylopine methiodide (0·0054%) were obtained. The amorphous residue still contained a small amount of both these alkaloids. The presence of magnoflorine or other alkaloids could not be detected. Fraction *E* (0·13 g) was dark brown and amorphous.

Characterization of the Isolated Substances

Dihydrosanguinarine: from chloroform–methanol needles of m.p. 188—189°C, undepressed in admixture with an authentic sample prepared from chelidonine[21]. Its UV spectrum, λ_{max} (log ε) 237 nm (4·57), 285 nm (4·59), 323 nm (4·21), λ_{min} 257 nm (4·21) and 311 nm (4·15) was identical with the spectrum published in ref.[22]. R_F values: 0·67 in S_1, 0·84 in S_2, 0·78 in S_3, 0·96 in S_5 0·98 in S_6 and 0·88 in S_{10} (violet fluorescent spot, orange colour formed in air). Oxidation to sanguinarine: the substance was dissolved in hot methanol, excess mercuric acetate dissolved in 10% acetic acid was added, and the mixture heated on a water bath for 10 minutes. Sodium formate was added, the mixture heated again and the reduced precipitated mercury filtered off. The filtrate was alkalinized with ammonia, the base extracted with ether, and ether evaporated. Crystallization from a hydrochloric acid solution in methanol gave sanguinarine chloride in the form of red needles, m.p. 284—285°C, undepressed in admixture with an authentic sample, with which it also had identical R_F values, *i. e.* 0·42 in S_{11}, 0·46 in S_{13} and 0·34 in S_{14} (orange fluorescent spot).

Dihydrochelerythrine: prisms of m.p. 161—162°C (chloroform–methanol), undepressed in admixture with an authentic sample. Its UV spectrum and R_F values were also identical with those of an authentic sample. Oxidation to chelerythrine and the conversion of the base to chloride were carried out in the above mentioned manner. The chelerythrine chloride obtained formed yellow needles of m.p. 201—202°C, the same as of an authentic sample. R_F values (in S_{11}, S_{13} and S_{14}) 0·11, 0·57 and 0·30, respectively, were also identical (yellow fluorescent spot).

Dihydrochelirubine: after two crystallizations from chloroform–methanol the crude preparation had m.p. 192—193°C, mixed melting point with an authentic sample was 193—195°C. According to thin-layer chromatography it contained trace amounts of dihydrosanguinarine. Its UV spectrum was identical with that of an authentic sample; so were the R_F values in four solvent systems. Oxidation of 2·1 mg of the substance in the above mentioned manner afforded 1·9 mg of base from which chloride was prepared which crystallized in the form of purple needles of m.p. 278—281°C (for chelirubine chloride ref.[23] gives m.p. 282—283°C), undepressed in admixture with authentic chelirubine chloride. Their identity was also confirmed by R_F values in S_{11}, S_{13} and S_{14}, which were 0·55, 0·57 and 0·66, respectively (purple fluorescent spot).

Substance X: a preparation was used isolated in a previous study[1] by chromatography of non-basic fractions on an alumina column. From chloroform–methanol it crystallized in the form of yellow needles, m.p. 291—292°C (capillary) or 304—306°C (Kofler block), optically inactive[1], insoluble in water, dilute acids and sodium hydroxide, poorly soluble in methanol, ethanol and

ether, better in chloroform. The solutions give a strong blue fluorescence. According to mass spectrometry it has the composition $C_{19}H_{13}NO_5$ (calculated 335·0794, found 335.0795). UV spectrum: λ_{max} (log ε) 225 nm (4·08), 347 nm (4·39) and 378 nm (4·13), shoulder at 258 nm (3·96) and 400 nm (3·98), λ_{min} 295 nm (3·71) and 371 nm (4·10). R_F values: 0·06 in S_1, 0·49 in S_2, 0·67 in S_4, 0·61 in S_5 and 0·73 in S_6 (blue fluorescent spot).

Magnoflorine iodide: m.p. 265—266°C (methanol), undepressed in admixture with an authentic sample, UV spectrum[24] and R_F values (0·64 in S_7, 0·53 in S_8. 0·54 in S_9, and 0·43 in S_{13}) were also identical with those of an authentic sample.

(—)-α-*Stylopine methiodide*: needles of m.p. 282—285°C (methanol), undepressed in admixture with an authentic specimen, $[\alpha]_D^{25}$ —125° ± 3° (*c* 0·13, methanol). R_F values, 0·45 in S_7, 0·42 in S_8, 0·72 in S_9, and 0·70 in S_{13}, were also identical with those of reference sample.

(—)-β-*Stylopine methiodide*: needles of m.p. 299—301° (methanol), undepressed in admixture with an authentic sample, $[\alpha]_D^{25}$ —120° ± 3° (*c* 0·13, methanol). R_F values, 0·50 in S_7, 0·49 in S_8, and 0·54 in S_{13} were also the same as the values of a reference sample.

Preparation of Dihydro Derivatives of Chelerythrine, Chelirubine, Chelilutine and Sanguilutine

Dihydro derivatives of the alkaloids mentioned were prepared by reduction of the chloride of the corresponding quaternary alkaloid with sodium borohydride, substantially in the same manner: the chloride was dissolved in a mixture of water and methanol (1 : 1) and excess sodium borohydride was added in portions. After about one hour's standing the separated product was filtered off under suction or strongly diluted with water and extracted with ether, and crystallized from chloroform–methanol. The spots of all substances mentioned were detected on Silufol plates both by inspection under UV light (violet fluorescence), or by leaving them to spontaneous oxidation (autooxidation) with air oxygen (during 1—2 h), which afforded a coloured spot of the initial quaternary alkaloid (the colour of the spot is given in brackets).

Dihydrochelerythrine (yield 93%): m.p. 161—163°C; UV spectrum: λ_{max} (log ε) 230 nm (4·62) 282 nm (4·72), shoulder at 325 nm (4·28), λ_{min} 254 nm (4·32). R_F values: 0·58 in S_1, 0·74 in S_2, 0·14 in S_3, 0·67 in S_5, 0·81 in S_6 and 0·67 in S_{10} (yellow).

Dihydrochelirubine (yield 94%): m.p. 198—199°C (ref.[25] gives for "dihydrobocconine" m.p. 206—207°C, uncorrected); UV spectrum: λ_{max} (log ε) 231 nm (4·59), 280 nm (4·52) and 338 nm (4·30), λ_{min} 255 nm (4·26) and 315 nm (4·09). R_F values: 0·62 in S_1, 0·79 in S_2, 0·64 in S_3, and 0·79 in S_{10} (purple).

Dihydrochelilutine (yield 87%): m.p. 136—137°C (capillary) or 132—135°C (Kofler block); UV spectrum: λ_{max} (log ε) 230 nm (4·52), 280 nm (4·56), and 325 nm (4·21), λ_{min} 255 nm (4·21) and 309 nm (4·11). R_F values: 0·41 in S_1, 0·67 in S_2, 0·14 in S_3 and 0·49 in S_{10} (yellow-orange).

Dihydrosanguilutine (yield 84%): m.p. 155—157°C (ref.[18] gives m.p. 154—155°C); UV spectrum: λ_{max} (log ε) 228 nm (4·61), 277 nm (4·67) and 327 nm (4·33), λ_{min} 254 nm (4·36) and 305 nm (4·17). R_F values: 0·21 in S_{10} (golden-yellow).

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Note added in proof: Applying the total synthesis of chelilutine and sanguilutine (Kessar S. V., Gupta Y. P., Dhingra K., Sharma G. S., Narula L.: Tetrahedron Lett. *1977*, 1459) was recently proved that both alkaloids have the methoxyl group in the position 5, like as chelirubine (Ishida T., Ueda E., Nakajima K., Ninomiya J., Naito T., Kiguchi T.: Tetrahedron Lett. *1975*, 319). From the study carried out it follows for dihydrochelirubine, dihydrochelilutine and dihydrosanguilutine the structure *IIc*, *IId* and *IIe*, resp., where $R^1 = OCH_3$, $R^4 = H$.