ALKALOIDS OF THE *Papaveraceae*. II.*

ON ALKALOIDS FROM *Argemone ochroleuca* SWEET

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Dedicated to Prof. Dr A. Okáč on the occasion of his 70th birthday.

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Argemone ochroleuca SWEET contains as its main alkaloids allocryptopine, protopine, and berberine. In a lower yield (−)-cheilanthifoline, sanguinarine, chelerythrine, coptisine, (−)-α-canadine methohydroxide, (−)-stylopine methohydroxide, and (−)-α-tetrahydropalmatine methohydroxide have been isolated.

Argemone ochroleuca SWEET, a one-year plant growing in the southern parts of North America, represents according to the new classification by Ownbey[1] an independent species closely related to *A. mexicana* L. which was named in older botanical literature[2] *A. mexicana* var. *ochroleuca* (SWEET) LINDL. (synonymum *A. barclayana* PENNY). The alkaloids of this plant were investigated by Giral and Sotelo[3] who isolated from it allocryptopine and protopine. Paper chromatography demonstrated the presence of berberine, coptisine and sanguinarine[4].

From the plants cultivated on the territory of Czechoslovakia we isolated ten alkaloids in crystalline form and identified them. The main fraction of tertiary nonphenolic bases was composed of allocryptopine and protopine, while benzophenanthridine alkaloids sanguinarine and chelerythrine were obtained in smaller amounts. From the fraction of phenolic bases (−)-cheilanthifoline (*I*) has been isolated which was identified on the basis of its mass, NMR, IR, and UV spectra, as well as its mixed melting point with an authentic preparation. The mass spectrum contains characteristic peaks at masses 325·1314 (M^+, for $C_{19}H_{19}NO_4$ calculated 325·1314), 324 (M-1), 176 (a) and 148 (b), in accordance with the literature data[5]. In the case of the compound labelled with deuterioethanol a shift of the ions M^+ and 176 takes place, but not in the case of ion 148. This alkaloid which was isolated for the first time from some species of *Corydalis*[6–8], was also recently found as a minor component in *A. grandiflora* SWEET[5]. From the fraction of quaternary protoberberines berberine was isolated as the main component while the presence of negligible

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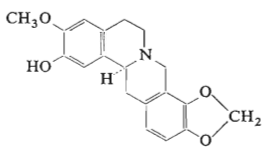
amount of coptisine was proved by its reduction and isolation in the form of tetrahydroderivative and identification by mixed melting point with an authentic sample.

In addition to the mentioned alkaloids the presence of highly polar bases was also proved, which could be extracted with chloroform in the form of their iodides. Fractional crystallisation of this fraction gave three quaternary alkaloids. The most abundant was (−)-α-canadine methiodide (*IIa*) which we found earlier in three species of *Eschscholtzia*[9] as the first case of its occurence in *Papaveraceae*. A minor part of quaternary iodides was composed of (−)-stylopine methiodide (*IIb*) which



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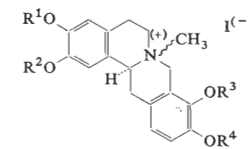
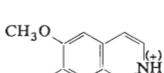
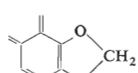


IIa, $R^1 + R^2 = CH_2$, $R^3 = R^4 = CH_3$
IIb, $R^1 + R^2 = R^3 + R^4 = CH_2$
IIc, $R^1 = R^2 = R^3 = R^4 = CH_3$



a



b

was determined recently as a natural alkaloid in *Glaucium corniculatum* CURT.[10]. (−)-α-Tetrahydropalmatine methiodide (*IIc*) which was found for the first time as a natural alkaloid in *Fagara capensis* THUNB. (*Rutaceae*)[11] was isolated in a negligible amount. All three mentioned quaternary alkaloids were identified on the basis of their IR and UV spectra, optical rotation value, mixed melting points with authentic preparations, and R_F values.

(+)-Tetrahydropalmatine methiodide which was prepared for comparison from (+)-tetrahydropalmatine by methylation with methyl iodide corresponded in its physical constants to the β-form which is more stable according to the literature[12] and which represents the main reaction product. The properties of diastereoisomeric α- and β-forms of (−)-tetrahydropalmatine methiodide (O,O'-dimethylcyclanoline iodide), which differ in their melting points, optical rotations and IR spectra, were described by Tomita and Kikuchi[12]. Analogous differences in the properties of α- and β-metho salts of canadine were already observed earlier[13]. From this point of view it is of interest that in the case of the metho salts of stylopine only one of the two possible forms was observed; the preparation obtained by methylation of (−)-stylopine with methyl iodide is identical in all its constants with the iodide of the natural alkaloid from *G. corniculatum*[10], *A. ochroleuca* and *A. platyceras*[14].

The main alkaloids present in *A. ochroleuca* and their quantitative representation show that this species is biochemically closely related to *A. mexicana* L.[15], confirming the assignment of this plant to the alliance *IVb* in the Stermitz classification of *Argemone* genus[16,17]. The finding of quaternary tetrahydroprotoberberine alkaloids is phytochemically remarkable, because except for the quaternary protoberberines and benzophenanthridines no other quaternary bases have been found up to now in the *Argemone* genus (an exception is argemonine methohydroxide isolated from *A. gracilenta* GREENE[18]), probably because the method used by the majority of authors caused them to escape attention. Their more general occurrence may be supposed on the basis of our more recent finding of (−)-platycerine methohydroxide, (−)-argemonine methohydroxide, and (−)-stylopine methohydroxide in *A. platyceras* LINK et OTTO, and (−)-β-scoulerine methohydroxide in *A. albiflora* HORNEM.[14].

EXPERIMENTAL

The melting points were determined both in capillaries and on Kofler block and they were not corrected. The mass spectra were measured on a mass spectrometer AEI-MS 902 at 70 eV, the NMR spectra on a Varian T-60 apparatus (tetramethylsilane as standard), the UV spectra on a Unicam SP 500 or a SP 700 spectrophotometer, and the IR spectra were recorded with an Infrascan Hilger and Watts. Paper chromatographic analyses were carried out on Whatman No 1 paper by the descending technique in butanol–acetic acid–water 10 : 1 : 3 (S_1) and the spots were detected on the basis of their fluorescence. For thin-layer chromatography silica gel containing calcium sulfate (5 : 1) was used, taking the following solvent combinations for development: cyclohexane–chloroform–diethylamine 7 : 2 : 1 (S_2) or 3 : 6 : 1 (S_3), benzene–ethanol–25% ammonia 100 : 20 : 1 (S_4), benzene–ethyl acetate–diethylamine 5 : 4 : 1 (S_5), ethanol–water–25% ammonia 15 : 9 : 1 (S_6), and 1-propanol–formic acid–water 12 : 1 : 7 (S_7). The spots were detected by potassium iodoplatinate or Dragendorff reagent.

Isolation of Alkaloids

The plants were cultivated in the Experimental Botanical Garden of the Medical Faculty in Brno and gathered on September 25, 1969 at the stage of unripe fruits. The plants were dried at room temperature. The dry, ground plant (5060 g) was extracted 7 times with methanol (total 140 l) in the cold. After evaporation of methanol the extract was transferred into 1% sulfuric acid and the alkaloids of the fractions *A*, *B*, *E* and *I* were separated in the usual manner[19]. The crude bases of the fraction A were separated[20] to fractions *ACa*, *ACb*, AD_1 and AD_2. Crystallisations of the bases of the fraction *ACa* and AD_1 from ether were employed for the separation of allocryptopine (3·57 g; 0·071% of the dry plant), m.p. 160—161°C (ethanol), and protopine (2·88 g; 0·057% of the dry plant), m.p. 206—207°C (chloroform–ethanol). The identity was in both cases corroborated by the mixed melting point with authentic specimens and on the basis of their IR and UV spectra and R_F values. From the mother liquors after crystallisation of these two alkaloids quaternary benzophenanthridine alkaloids were separated in the form of non-basic pseudocyanides. The bases prepared from this fraction afforded by a further separation on alumina under usual conditions[21] sanguinarine (48 mg, R_F 0·46 in S_1, orange fluorescence; pseudocyanide m.p. 238—239°C from chloroform–ethanol) and chelerythrine (12 mg, R_F 0·55 in S_1, yellow fluorescence; pseudocyanide m.p. 260—261°C from chloroform–ethanol). The mixed melting points of the prepared pseudocyanides with authentic samples were undepressed. The fraction *ACb* gave on crystallisation from methanol cheilanthifoline (71 mg; 0·0015% of the dry plant) and a nitrogen-free compound of m.p. 243—246°C (31 mg) which was not further investigated. From the fraction AD_2 a nitrogen-free compound was obtained on crystallisation

from ether in addition to negligible amounts of allocryptopine and protopine. It weighed 37 mg, m.p. 278—280°C, composition $C_{30}H_{50}O$ (m.w. determined by mass spectrometry was 426·3877, calculated value 426·3861), which is probably a triterpene; according to its IR spectrum in chloroform it contains a keto group (1 725 cm^{-1}).

The fraction *B* afforded on crystallisation from hydrochloric acid 0·60 g of berberine chloride (total yield, including the fractions obtained from fractions *E* and *I*, was 0·77 g, 0·015% of the dry plant), R_F 0·56 in S_1, yellow-green fluorescence, from which a tetrahydro derivative of m.p. 163—165°C (ethanol) was prepared by reduction with zinc and hydrochloric acid. It melted undepressed on admixture of an authentic specimen.

The fraction *E* after the separation of small amount of berberine in the form of a chloride contained only non-alkaloid substances. From the concentrated chloroform solution of the fraction *I* (iodides of quaternary bases) 210 mg of berberine iodide crystallised out, m.p. 259—262°C, identified by its UV spectrum and the R_F value in S_1. From the mother liquor another 72 mg of yellow protoberberine bases were isolated in the conventional manner, which represented a mixture of coptisine and berberine (a golden-yellow fluorescing spot of R_F 0·44 and a yellow-green fluorescing spot of R_F 0·56 in S_1). From this mixture tetrahydro derivatives were prepared on reduction with zinc and hydrochloric acid, from which tetrahydrocoptisine, m.p. 218°C was separated by crystallisation from chloroform–ethanol. It melted undepressed on admixture of authentic (±)-stylopine. From the mother liquor tetrahydroberberine was isolated. The remaining fraction *I* afforded on crystallisation from chloroform–methanol–ether a fraction which according to mass spectrometry contained predominantly canadine methiodide (peaks at *m/e* 339 [M-CH_3I], 176, 174, 164, 149, 142 [CH_3I] and 127 [I]) and small amounts of stylopine methiodide (characteristic peaks at *m/e* 323 [M-CH_3I], 148) and traces of tetrahydropalmatine methiodide (characteristic peak at *m/e* 355 [M-CH_3I]). Systematic crystallisation of fraction *I* from methanol or methanol–ether gave (—)-α-canadine methiodide (94·1 mg, 0·002% of the dry plant), (—)-stylopine methiodide (31·8 mg, 0·0006% of the dry plant), and (—)-α-tetrahydropalmatine methiodide (8·2 mg, 0·0002% of the dry plant).

(—)-*Cheilanthifoline*: needles, m.p. 183—184°C (methanol), undepressed on admixture of an authentic sample (m.p. 183—184°C) (refs[10,22]), $[\alpha]_D^{20}$ −331° ± 15° (*c* 0·1, methanol); literature gives m.p. 183—184°C (ref.[10]) or 200—201°C (ref.[22]) and $[\alpha]_D^{20}$ −311° (methanol)[10]. The mass spectrum with main peaks at *m/e* 325 (M^+), 176 and 148, and the NMR spectrum ($CDCl_3$), τ 6·14 (OCH_3), 4·07 (O_2CH_2), 3·43, 3·36 and 3·20 (aromatic protons) agree with the literature data[5,22]. The IR spectrum (chloroform), ν(OH) 3 530 cm^{-1}, and the UV spectrum (ethanol), λ_{max} 206 nm (log ε 4·75), shoulder at 234 nm (log ε 3·93), λ_{max} 288 nm (log ε 3·80), λ_{min} 256 nm (log ε 2·91) also correspond to the literature data[22]. R_F values 0·23 (S_2), 0·70 (S_3), 0·71 (S_4), and 0·75 (S_5) were identical with those of an authentic sample. With conc. sulfuric acid it gives orange spots turning to yellow-brown (identically as with the authentic specimen).

(—)-α-*Canadine methiodide*: From methanol it crystallises in leaflets, m.p. 160—164°C, solidifying about 180°C, melting again at 210—215°C, solidifying about 230°C and melting again at 249—251°C under decomposition; in admixture with an authentic specimen[9] it melted undepressed and behaved in the same manner. A preparation crystallised from water melted at 218 to 220°C, solidifying at about 230°C (transformation of the α-form to the β-form) and remelted at 252—253°C (decomp.); $[\alpha]_D^{21}$ −114° ± 5° (*c* 0·2, methanol). All these properties coincide with the data from literature[9,13]. The UV (methanol) and IR (KBr) spectra were identical with those of an authentic samples[9]; so were the R_F values (0·63 in S_6 and 0·79 in S_7) and the colour reactions.

(—)-*Stylopine methiodide*: From methanol the m.p. was 295—298°C (Kofler block) or 275 to 276°C (capillary), undepressed on admixture of an authentic sample[10]; $[\alpha]_D^{21}$ −123° ± 3° (*c* 0·1,

methanol), UV spectrum (methanol), IR spectrum (KBr), R_F values (0·56 in S_6 and 0·79 in S_7), as well as the characteristic colour reactions were the same as in the case of an authentic preparation[10].

(−)-α-*Tetrahydropalmatine methiodide*: M.p. (from methanol–ether) 203—205°C (capillary), or 204—208°C (Kofler block), undepressed on admixture of an authentic sample[12], $[\alpha]_D^{22}$ −99° ± ± 20° (*c* 0·04, methanol) (due to the low concentration of the solution this value should be considered as approximate only); literature gives m.p. 203—204°C (see[11]) or 208°C (see[12]), and appreciably different optical rotations: $[\alpha]_D^{11}$ −73·04° (methanol)[12] or $[\alpha]_D^{24}$ −258·2° (methanol[11]) The UV spectrum (methanol), shoulder at 232 nm (log ε 4·28), λ_{max} 284 nm (log ε 3·77), λ_{min} 257 nm (log ε 2·77), as well as the IR spectrum (KBr) and the R_F values 0·61 (S_6) and 0·71 (S_7) were identical as in the case of an authentic specimen[12] or the literature data[11,12].

(+)-β-*Tetrahydropalmatine methiodide*: (+)-Tetrahydropalmatine (50 mg), isolated from the tubers of *Corydalis cava*[23], was methylated with methyl iodide (0·5 ml) in methanol–ether. The separated product was crystallised from methanol, m.p. 249—251°C (capillary) or 263—265°C (Kofler block), identical as in the case of authentic (−)-β-tetrahydropalmatine methiodide (β-(−)-O,O′-dimethylcyclanoline iodide)[12], $[\alpha]_D^{25}$ +109° ± 5° (*c* 0·14, methanol). The UV spectrum (methanol) was identical with that of the (−)-α-form, the IR(KBr) spectrum was the same as that of an authentic sample of the (−)-β-form[12]. The R_F values are identical with those of the (−)-α-form (see above) and an authentic sample of the (−)-β-form.

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REFERENCES

1. Ownbey G. B.: *Monograph of the Genus* Argemone *for North America and the West Indies. Memoirs of the Torrey Botanical Club*, Vol. 21, No 1. The Seeman Printery, Durham, N. C. 1958.
2. Fedde F. in the book: *Das Pflanzenreich*-Regni vegetabilis conspectus (A. Engler, Ed.), Part IV, Bd. 104. Leipzig 1909.
3. Giral F., Sotelo A.: Ciencia (Mex.) *19*, 67 (1959).
4. Hakim S. A. E., Mijović V., Walker J.: Nature *189*, 198 (1961).
5. Benn M. H., Mitchell R. E.: Phytochemistry *11*, 461 (1972).
6. Manske R. H. F.: Can. J. Res. B *14*, 347 (1936).
7. Manske R. H. F.: Can. J. Res. B *14*, 354 (1936).
8. Manske R. H. F.: Can. J. Res. B *18*, 100 (1940).
9. Slavík J., Dolejš L., Sedmera P.: This Journal *35*, 2597 (1970).
10. Novák V., Dolejš L., Slavík J.: This Journal *37*, 3346 (1972).
11. Calderwood J. M., Finkelstein N., Fish F., Parfitt R. T.: Phytochemistry *10*, 682 (1971).
12. Tomita M., Kikuchi T.: Yakugaku Zasshi *77*, 73 (1957); Chem. Abstr. *51*, 9647 (1957).
13. Jowett H. A. D., Pyman F. L.: J. Chem. Soc. *103*, 290 (1913).

14. Slavík J., Haisová K., Slavíková L.: Unpublished results.
15. Slavíková L., Slavík J.:This Journal *21*, 211 (1956); Chem. listy *49*, 1546 (1955).
16. Stermitz F. R. in the book: *Recent Advances in Phytochemistry*, Vol. 1. (T. J. Mabry, R. E. Alston, V. C. Runeckles, Eds) Appleton-Century-Crofts, New York 1968.
17. Stermitz F. R., Nicodem D. E., Wei C. C., McMurtrey K. D.: Phytochemistry *8*, 615 (1969).
18. Stermitz F. R., McMurtrey K. D.: J. Org. Chem. *34*, 555 (1969).
19. Slavíková L., Slavík J.: This Journal *31*, 3362 (1966).
20. Slavík J., Slavíková L.: This Journal *26*, 1839 (1961).
21. Slavík J., Slavíková L.: This Journal *25*, 1667 (1960).
22. Tani Ch., Imanishi I., Nishijo J.: Yakugaku Zasshi *90*, 1028 (1970).
23. Slavík J., Slavíková L.: Unpublished results.

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