ALKALOIDS OF THE *Papaveraceae*. XLVIII.*

(−)-STYLOPINE METHOHYDROXIDE, A NEW ALKALOID FROM *Glaucium corniculatum* CURT.

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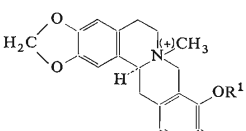
Received November 1st, 1971

From the highly polar fraction of alkaloids from *Glaucium corniculatum* CURT. (−) stylopine methohydroxide and (−)-β-canadine methohydroxide have been isolated in the form of iodides. Their mass spectra have been also investigated.

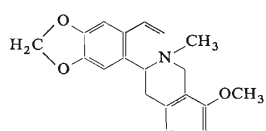
From the extract of *Glaucium corniculatum* CURT. the alkaloid allocryptopine was isolated[1,2] as the main component in addition to a lesser amount of protopine. Further[1] (−)-chelidonine, (+)-corydine, (+)-isocorydine, chelerythrine and sanguinarine were also isolated and chelirubine, coptisine and berberine were detected in trace amounts. In addition to this the presence of highly polar, ether insoluble basic components was also detected[1], which are the object of this study. Using conventional procedures[3] we isolated a fraction of quaternary bases in the form of their iodides, from which we separated by crystallisation (−)-stylopine methiodide (*Ia*) and (−)-β-canadine methiodide (*Ib*). (−)-Stylopine methiodide (yield 0·001% of the dry plant) was identified by direct comparison of the methiodide prepared from authentic (−)-stylopine. (−)-β-Canadine methiodide represents the main alkaloid (yield 0·008% of the dry plant) of the quaternary fraction. UV, IR, and mass spectra of this substance are identical with those of authentic (−)-α-canadine methiodide[4]; from the higher melting point and optical rotation it follows that it is the β-form[5,6]. The structure of *Ib* was proved on the basis of Hofmann degradation to (±)-tetrahydroberberinemethine[4] (*II*).

During the measurement of their mass spectra the iodides *Ia* and *Ib* split off methyl iodide pyrolytically under formation of tertiary bases. The mass spectrum of *Ia* displays strong peaks at masses 323 (20%, M-CH_3I), 322 (14%), 176 (3%), 174 (12%, *a*) 148 (100%, *b*, $R^1 + R^2 = CH_2$), 142 (37%, CH_3I), 127 (13%, I), 91 (19%), and 81 (14%). In the spectrum of *Ib* the main characteristic ions had the following masses: 339 (50%, M—CH_3I), 338 (32%), 176 (12%), 174 (25%, *a*), 164 (86%, *b*, $R^1 = R^2 = CH_3$), 149 (100%, *b*-15), 142 (85%, CH_3I), and 127 (27%, I). The spectra of both substances are analogous, to a certain extent, with those of stylopine or canadine (tetrahydroberberine).

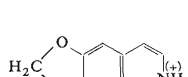
* Part XLVII: This Journal *37*, 2804 (1972).



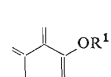
Ia, $R^1 + R^2 = CH_2$
Ib, $R^1 = R^2 = CH_3$



II



a



b

From the fraction of non-quaternary bases soluble in ether all alkaloids described earlier[1,2] as occurring in this plant were isolated. In addition to this two additional phenolic bases were also isolated, of m.p. 190°C and 237°C, which could not be further studied because of their minute quantity. In the fraction of quaternary protoberberines the presence of coptisine and berberine was demonstrated. After the reduction of this mixture to tetrahydroderivatives crystalline tetrahydrocoptisine was isolated which was identified on the basis of its mixed melting point with (±)-stylopine. While (−)-β-canadine methohydroxide was already discovered in nature earlier (for example[6]; the α-form occurs in plants more frequently, for example[4,5]), the discovery of (−)-stylopine methohydroxide in *G. corniculatum* represents the first case of the occurrence of this substance as a natural alkaloid.

EXPERIMENTAL

The melting points were determined both in capillaries and on a Kofler block and they were not corrected. The mass spectra were measured on a MS 902 apparatus at the temperature of the ionic source 220°C. The UV spectra were taken on a Unicam SP 500 and the IR spectra on an Infrascan, Hilger and Watts apparatus. Thin-layer chromatography was carried out on silicagel bound with gypsum (5 : 1) in the following solvent systems: cyclohexane–diethylamine 9 : 1 (S_1), cyclohexane–chloroform–diethylamine 7 : 2 : 1 (S_2), 5 : 4 : 1 (S_3), and 4 : 5 : 1 (S_4), hexane–chloroform–methanol 5 : 4 : 1 saturated with formamide (S_5), and ethanol–water–25% ammonia 15 : 9 : 1 (S_6); detection with potassium iodoplatinate (the colours after detection are given in brackets). Paper chromatography was carried out on paper Whatman No 1, descending method, in n-butanol–acetic acid–water 10 : 1 : 3 (S_7); fluorescent spots were detected under UV light, other spots with Dragendorff reagent. Known alkaloids isolated in this study were identified on the basis of their mixed melting points (using authentic samples) and R_F values.

Material. The plants were cultivated in the Experimental Botanical Garden, Medical Faculty, Brno, and they were harvested during flowering of the period of unripe fruits, on July 1st, 1966. The material was dried at room temperature.

Isolation of alkaloids. The dried and ground plant (5160 g) was extracted at room temperature with 7 portions of methanol (total 105 l). The extract was worked up in the usual manner and

from the extract alkaloid fractions[3] *A*, *B*, *E*, and *J* were obtained. Crude bases of fraction *A* (14·75 g) were separated[7] to fractions AC_1, AC_2, AD_1, and AD_2. From fraction AC_1 (+)-corydine was separated first in the form of weakly soluble hydrochloride and from the mother liquor (+)-isocorydine was obtained on crystallisation of bases from ether. In the same manner corydine and isocoryd ne were separated from the bases of fraction AC_2. From the mother liquor after isocorydine another unidentified base was obtained which was purified by repeated crystallisation from ethanol. Yield 1 mg, m.p. 190°C, R_F 0·08 (S_2), 0·18 (S_3), and 0·30 (S_4) (white-grey spot). Total yield of (+)-isocorydine (m.p. 149—150°C, from ether) was 0·37 g (0·007% of the plant); yield of (+)-isocorydine (m.p. 184°C, ethanol), including a small amount obtained from fraction AD_2 was 0·42 g (0·008% of the plant). From non-phenolic bases of fraction AD_1 the predominant part of allocryptopine (5·92 g, 0·115% of the plant; m.p. 160°C from ethanol) and protopine (4·28 g, 0·083% of the plant; m.p. 207—208°C from chloroform–ethanol) was separated by crystallisation from ether, and from the residual bases quaternary benzophenanthridine bases were obtained in the form of *ps*-cyanides. Chromatography of this fraction (17·8 mg of bases) in S_5 and S_7 demonstrated chelerythrine (R_F 0·47 and 0·55, resp., yellow fluorescence), sanguinarine (R_F 0·77 and 0·46, resp., orange fluorescence), and traces of chelirubine (R_F 0·88 and 0·57 resp., purple fluorescence). Crystallisation of the bases obtained from the filtrate after *ps*-cyanides from dilute hydrochloric acid separated (—)-chelidonine in the form of a weakly soluble hydrochloride (yield of the base 0·88 g, 0·017% of the plant; m.p. 136°C from aqueous ethanol). In the amorphous residue of the bases of fraction AD_1 (0·09 g) only traces of the mentioned alkaloids were detected in systems S_1 and S_2. Fraction AD_2 gave on crystallisation from ether a small amount of isocorydine and 5 mg of an unidentified phenolic base, which after a double crystallisation from ethanol had m.p. 235—237°C, R_F values 0·10 in S_2, 0·20 in S_3, and 0·33 in S_4 (blue-white spot). In amorphous phenolic bases from fractions AC_1, AC_2, and AD_2 (0·23 g) the presence of four additional unidentified bases was detected of R_F values (in S_2, S_3, and S_4, respectively) 0·02, 0·04, and 0·05 (yellow-white), 0·07, 0·11, and 0·18 (blue-white), 0·29, 0·43, and 0·69 (white-grey), and (in S_1 and S_2, resp.) 0·59 and 0·76 (brown-yellow).

Yellow bases of fraction *B* (13·8 mg) formed two spots in system S_7, corresponding to coptisine (R_F 0·45, golden-yellow fluorescence) and berberine (R_F 0·56, green-yellow fluorescence). Reduction with zinc in dilute hydrochloric acid gave tetrahydro derivatives which on crystallisation from ether gave 9·4 mg of tetrahydrocoptisine, m.p 218°C (chloroform–ethanol), undepressed on admixture of authentic (±)-stylopine. In the mother liquors chromatography in S_1 and S_2 demonstrated in addition to the remains of stylopine (R_F 0·58 and 0·81 resp.) also the presence of tetrahydroberberine (R_F 0·51 and 0·76 resp.).

The amorphous fraction *E* (2·02 g) contained predominantly substances which were not alkaloids. Chromatography in system S_6 demonstrated the presence of trace amounts of two alkaloids which by their R_F values coincided with stylopine methiodide and canadine methiodide. The crude fraction *J* (6·79 g), also containing predominantly non-alkaloidal substances, was dissolved in boiling water, filtered, and, after addition of potassium iodide, re-extracted with chloroform. The residue after evaporation of chloroform was dissolved in methanol and concentrated to give crystalline (—)-stylopine methiodide (50 mg). Further crystallisations of the mother liquors gave a larger amount of crystalline fractions of non-alkaloid nature which were not further investigated. From the concentrated mother liquor 0·39 g of (—)-β-canadine methiodide crystallised out. In the non-crystalline residue (0·03 g) the presence of a third quaternary base has been demonstrated in addition to the residues of the mentioned two alkaloids. Its R_F value was 0·09 in S_6 (brown-violet spot).

(—)-*Stylopine methiodide* was crystallised from methanol, m.p. 297—299°C (Kofler) or 278 to 279°C (capillary), undepressed on admixture of an authentic specimen, very weakly soluble

even in boiling methanol; $[\alpha]_D^{23}$ −123° ± 5° (*c* 0·13, methanol). Authentic (−)-stylopine methiodide was prepared by methylation of (−)-stylopine with methyl iodide in chloroform solution; m.p. in capillary 277−278°C (methanol), $[\alpha]_D^{23}$ −120° ± 5° (*c* 0·13, methanol). UV spectrum (methanol), λ_{max} 291 nm (log ε 3·96), λ_{min} 262 nm (log ε 3·35), shoulder at 230 nm (log ε 4·22), identical with the spectrum of an authentic preparation. The IR spectra of both samples were also identical (in nujol). The R_F value 0·51 (violet-brown spot) in S_6 is identical with the value of the authentic sample. With concentrated sulfuric acid it gives a light violet colour, with Erdmann reagent a strongly green-blue colour, changing to aquamarine, with conc. nitric acid a yellow colour; the same colour reactions are given by the authentic sample.

(−)-β-*Canadine methiodide* crystallised from water, m.p. 263−265°C (Kofler) or 260−261°C (capillary); well soluble in methanol; $[\alpha]_D^{23}$ −130° ± 3° (*c* 0·22, methanol). Literature[5] gives m.p. 264°C; the value of the optical rotation of β-methiodide could not be found in the literature. For the methochloride the value of $[\alpha]_D$ was in the literature[5,6] −160·9° and −158° resp. (in water). From these data the value for iodide was calculated approximatively: $[\alpha]_D$ −135°. The mixture of (−)-β-canadine methiodide with authentic (−)-α-canadine methiodide[4] (m.p. 220°C) in a capillary sinters at 215−220°C, but does not melt (transformation of the α-form to the more stable β-form[5]), m.p. 260−261°C under decomposition. The UV spectrum in methanol, λ_{max} 286 nm (log ε 3·73), λ_{min} 258 nm (log ε 2·80), shoulder at 235 nm (log ε 4·10), is identical with that of authentic (±)-tetrahydroberberine methiodide, as are their spectra in nujol. The R_F value, 0·56, (violet-brown spot), is identical with that of (−)-α-canadine methiodide. With conc. sulfuric acid it remains colourless, with Erdmann reagent it gives a brown coloration, with conc. nitric acid a yellow coloration. (−)-α-Canadine methiodide behaves in the same manner.

Hofmann Degradation of (−)-β-Canadine Methiodide

(−)-β-Canadine methiodide (62·7 mg) was refluxed with 5 ml of a 20% potassium hydroxide solution in methanol for 5 hours. From the reaction mixture 40·0 mg (87%) of a substance were isolated in the conventional manner[4], which after crystallisation from methanol melted at 114 to 115°C, undepressed on admixture of authentic (±)-tetrahydroberberinemethine[4] (m.p. 114 to 115°C). The UV spectrum (methanol), λ_{max} 264 nm (log ε 4·04) and 302 nm (log ε 3·74), λ_{min} 246 nm (log ε 3·71) and 291 nm (log ε 3·67), as well as the R_F values in S_1 (0·57) and S_2 (0·82) are identical with the values of the authentic sample.

For the measurement of the IR spectra our thanks are due to Mrs H. Škamradová, Chemical Institute, Palacký University, Olomouc, and for the UV spectra we thank Mrs J. Bochořáková, Department of Medical Chemistry, Purkyně-University, Brno.

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Translated by Ž. Procházka.