ON ALKALOIDS FROM *Papaver pseudocanescens* M. POP.*

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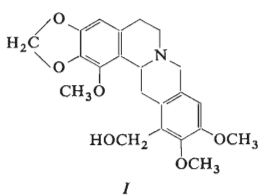
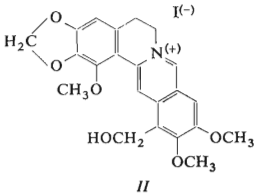
From *Papaver pseudocanescens* M. POP. mecambridine, alkaloid PO-5, protopine, cryptopine, amurensine, amurensinine and a new quaternary alkaloid mecambridine methohydroxide have been isolated.

Papaver pseudocanescens M. POP. is a perennial septentrional species of poppy of the *Scapiflora*[1] section. Nothing was known until recently of the alkaloids of this plant except for the presence[2] of papaverrubines B, D and E. Prior to the termination of our present work Pfeifer and Thomas published a paper[3] describing the isolation of mecambridine (oreophiline), alkaloid PO-5 (alborine), protopine, amurensine, papaverrubines C, D, and E and proving the presence of traces of rhoeadine. The plants grown in our country were characterised by a relatively very low content of total alkaloids (0·02%). In accordance with the literature[3] we also separated mecambridine as the main alkaloid. This alkaloid was isolated first from *Meconopsis cambrica* (L.) VIG.[4,5] and it was found later in *P. oreophilum* F. J. RUPR. (ref.[6]), and in a larger number of other *Papaver* species of the sections *Pilosa*, *Scapiflora*, and *Macrantha*. The originally proposed structure[7] was later[8–10] revised and formula *I* proposed. We isolated from the mother liquors after mecambridine a small amount of a strongly polar alkaloid in the form of its iodide, which was found identical with the iodide of alkaloid PO-5[11] ("alborine"[12]) (*II*) (refs[9,10]). It seems probable



I

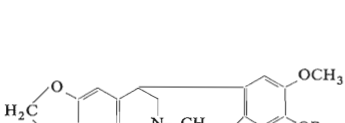


II

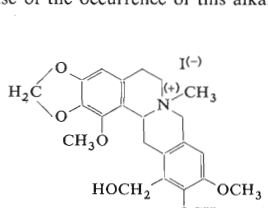
* Part LIII in the series Alkaloids of the *Papaveraceae*; Part LII: This Journal *38*, 3514 (1973).

that this substance is an artifact formed on oxidation of mecambridine with air oxygen[12]. We also isolated in low yields amurensine[13] (*IIIa*), protopine and two additional alkaloids, amurensinine[13] (*IIIb*) and cryptopine, which had not been found in this plant so far. In addition to this we also proved the presence of trace amounts of not identified papaverrubines. On the other hand, we were unable to prove the presence of even traces of rhoeadine[3].

From the fraction of strongly polar alkaloids we isolated a quaternary base in the form of its iodide which according to IR and UV spectra, melting point determination and mixed melting point and optical rotation value was identical with (−)-mecambridine methiodide (*IV*). This is the first case of the occurrence of this alkaloid as a natural substance.



IIIa, R = H
IIIb, R = CH_3



IV

EXPERIMENTAL

The melting points (uncorrected) were determined both in capillaries and on a Kofler block. The mass spectrum was measured with an AEI-MS 902 Spectrometer, the IR spectra with an Infrascan Hilger and Watts apparatus, and the UV spectra (in methanol) on a Unicam SP 500 spectrophotometer. For thin layer chromatography silica gel with gypsum (5 : 1) was employed with the following solvent systems: cyclohexane–diethylamine 9 : 1 (S_1), cyclohexane–chloroform–diethylamine 7 : 2 : 1 (S_2), 5 : 4 : 1 (S_3), and 2 : 7 : 1 (S_4), methanol–diethylamine 8 : 2 (S_5), methanol–chloroform–diethylamine 2 : 7 : 1 (S_6), benzene–acetone–methanol 7 : 2 : 1 (S_7), ethanol–water–25% ammonia 15 : 9 : 1 (S_8), and 1-propanol–water–85% formic acid 7 : 2 : 1 (S_9). Detection of the fluorescing spots was carried out under UV light, other spots were detected with Dragendorff reagent and potassium iodoplatinate, resp.

Isolation of Alkaloids

The plants were cultivated in the Experimental Botanical Garden, Medical Faculty, Brno, from seeds obtained from the Botanical Garden of Moscow, USSR. The plants were harvested in the third year of vegetation during the period of flowering or of unripe fruits on July 7, 1967. The material was dried at room temperature. The identity of the plants was checked according to description in the literature[1].

Dry ground plant (8 525 g) was extracted five times with methanol (total 200 l) at room temperature. The solvent was evaporated from the combined extracts. In order to prevent the decomposition of the alkaloids sensitive to mineral acids, dilute acetic acid was employed during sub-

sequent isolation procedures in a concentration not exceeding 2%, and the work was carried out in the cold. Applying the conventional procedure[14,15] fractions *A*, *B*, *I* and *E* were obtained. Fraction *A* was dissolved in 2% acetic acid, a potassium chloride solution added, and the mixture extracted with chloroform to separate the chloroform soluble (*AC*) and chloroform insoluble (*AD*) hydrochloride fraction. Both these fractions were then separated[14] to substances of non-phenolic (AC_1 and AD_1) and phenolic (AC_2 and AD_2) character. From the bases of fraction AC_1, mecambridine was obtained by crystallisation from ether (total yield 0·73 g; 0·009%). The remaining bases were dissolved in 2% acetic acid, alkalised with ammonia and the tertiary bases extracted with ether. The aqueous layer was then acidified with dilute sulfuric acid, a potassium iodide solution added and the mixture extracted with chloroform to afford 79·2 mg of the iodide of alkaloid PO-5 (total yield including the material separated from fraction *I* was 107·6 mg; 0·0013%). From the fraction of tertiary bases soluble in ether amurensine (6·2 mg, 0·0001%) was separated by crystallisation after the separation of a small amount of mecambridine. From the amorphous residue 80 mg of a substance of non-alkaloid nature was isolated, and from the residue of bases, transformed to hydriodides, 70 mg of amurensinine hydriodide were obtained by crystallisation from methanol–ether (calculated as base, 51 mg; 0·0006%). The remaining amorphous bases (0·11 g) also contained according to thin layer chromatography predominantly amurensinine in addition to trace amount of mecambridine, amurensine, cryptopine and protopine and a small amount of two undentified alkaloids of R_F (in S_1) 0·09 and 0·19 or in S_2 0·30 and 0·43. The AC_2 fraction contained only traces of the same bases which were found in the fraction AC_1, and in addition to this the presence of trace amounts of unidentified papaverrubines was also proved by thin layer chromatography (detection with hydrochloric acid vapours). Fractional crystallisation of fraction AD_1 from ether gave cryptopine (38·4 mg; 0·0005%) and protopine (24·4 mg; 0·0003%). In the amorphous residue of bases (22·2 mg) the residues of both above mentioned alkaloids were demonstrated by thin layer chromatography and a small amount of amurensinine and traces of papaverrubines. The fractions AD_2 (50 mg) and *B* (1·2 mg) were not alkaloids.

After further purification and elimination of the major part of the non-alkaloidal material fraction *I* (2·95 g) was crystallised from a methanol–ether mixture to afford 28·4 mg of the iodide of alkaloid PO-5. The amorphous residue was dissolved in dilute sulfuric acid and on addition of 20% sodium perchlorate solution the poorly soluble perchlorates of quaternary bases were precipitated. After converting the perchlorates to iodides their crystallisation from methanol–ether gave mecambridine methiodide (41·1 mg; 0·0005%).

Fraction *E* (1·12 g) was amorphous. After elimination of non-alkaloidal material 0·27 g of amorphous bases were obtained which according to thin layer chromatography contained as the main component a base of R_F value 0·05 (S_2), 0·09 (S_3), 0·94 (S_6), 0·26 (S_7), and 0·82 (S_8) in addition to a base of R_F 0·63 (S_6) and 0·70 (S_8) and two strongly polar alkaloids of R_F 0·04 and 0·16 in S_6, and 0·08 and 0·14 in S_8.

Characterisation of the Isolated Alkaloids

(—)-*Mecambridine:* needles, m.p. 179—180°C (ethanol–ether), undepressed in admixture with an authentic sample[5], $[\alpha]_D^{23}$ −245° ± 2° (*c* 0·20, methanol). The UV spectrum and the R_F values (0·14 in S_1, 0·36 in S_2) were identical with the values of the authentic specimen. In air it is slowly oxidized to alkaloid PO-5. From a pure crystalline preparation of mecambridine kept in darkness for over a year we isolated alkaloid PO-5 in the form of its iodide in 4% yield. Methiodide: 69·8 mg of mecambridine were dissolved in 8 ml of methanol, 0·3 ml of methyl iodide were added and the mixture evaporated after three days standing (yield 91·3 mg, quantitative). The crude product was crystallised from methanol by addition of ether; m.p. 206—207°C, $[\alpha]_D^{23}$ −171° ± 10° (*c* 0·14, methanol). Literature[16] gives m.p. 207—209°C.

Alkaloid PO-5: the iodide crystallised from methanol in yellow needles which sinter at 242 to 244°C, darken over 250°C, but do not melt below 360°C. This behaviour corresponds to the literature data[3,12]. UV spectrum, λ_{max} (log ε) 246 nm (4·43), 264 nm (4·47), 291 nm (4·65) and 330 nm (4·38), λ_{min} 241 nm (4·40), 253 nm (4·39), 271 nm (4·40), and 315 nm (4·37). It is in agreement with the literature data[3,11]. With concentrated sulfuric acid it gave a yellow-greenbrown colour, with conc. nitric acid a yellow colour. Perchlorate crystallised from methanol gave yellow needles, sintering at 228°C, m.p. 255—258°C (decomposition). The IR spectrum (in KBr) was identical with that of an authentic sample, as also were the R_F values: 0·09 in S_5 and 0·39 in S_8 (blue-greenish fluorescence).

Reduction to (±)-mecambridine: 25·4 mg of the iodide of alkaloid PO-5 were dissolved in hot water and reduced with zinc in dilute hydrochloric acid. After filtration the solution was alkalised with ammonia and extracted with ether. The residue (20·6 mg; 93%), after evaporation of ether, was crystallised from methanol–ether mixture, m.p. 189—192°C; literature gives m.p. 175—177°C[9] or 177°C[12]. The UV spectrum, R_F values, and colour reactions were identical as in the case of natural (—)-mecambridine.

Amurensine: m.p. 206—208°C (methanol–ether–hexane mixture), mixed melting point with an authentic specimen melting at 208—209°C was undepressed. The UV spectrum, λ_{max} (log ε) 295 nm (3·96), λ_{min} 262 nm (3·23), coincided with the literature data[13], the R_F values, 0·07 (S_1), 0·13 (S_2), 0·26 (S_3), 0·59 (S_4) and 0·18 (S_7), were identical with those of an authentic sample, as also were the colour reactions with conc. sulfuric acid (yellow), Erdmann reagent (brown-violet), Fröhde reagent (brown-violet), and conc. nitric acid (brown-red).

Amurensinine: after crystallisation from ether, m.p. 136—138°C (Kofler block), undepressed on admixture of an authentic specimen (m.p. 137—139°C, Kofler block), $[\alpha]_D^{22}$ —142° ± 5° (*c* 0·10, methanol). Literature[13] gives m.p. 162—164°C or [16] 143—144°C and $[\alpha]_D$ in methanol —175° (*cf.*[13]) or —108° (*cf.*[16]). The mass spectrum with characteristic peaks at *m/e* 339 (M^+), 338 (M-1), 296 (M-43) and 188 was identical with the spectrum of amurensinine (*cf.*[17]). The identity was confirmed by IR spectroscopy (in KBr), UV spectrum, λ_{max} (log ε) 294 nm (3·91), λ_{min} 264 nm (3·12), R_F values 0·32 (S_1), 0·55 (S_2) and 0·20 (S_7) and colour reactions: with conc. sulfuric acid it gave a brown-red colour, turning green, with Erdmann reagent it gave a green colour turning yellow-brown, with Fröhde reagent the colour was brown, and with conc. nitric acid red-brown, turning yellow-brown. Hydriodide (from methanol–ether), m.p. 236—245°C (decomp.; Kofler block).

Cryptopine: m.p. 219—220°C (chloroform–ethanol), undepressed in admixture with an authentic specimen. UV spectrum, R_F values (0·25 in S_1, 0·59 in S_2) and colour reactions identical to those of an authentic sample.

Protopine: m.p. 205—206°C, undepressed in admixture with an authentic specimen. The UV spectrum, R_F values (0·40 in S_1, 0·64 in S_2) and colour reactions were also identical.

(—)-Mecambridine methohydroxide: iodide, m.p. 203—206°C (methanol–ether), undepressed in admixture of a sample prepared from (—)-mecambridine, easily soluble in cold methanol, insoluble in ether, $[\alpha]_D^{23}$ —169° ± 10° (*c* 0·10, methanol). IR spectrum (in KBr) and UV spectrum, λ_{max} (log ε) 286 nm (3·79), λ_{min} 261 nm (3·43), were identical with the spectra of an authentic specimen, as also were R_F values in S_5 (0·08), S_8 (0·34), and S_9 (0·69) (blue-violet fluorescence; after detection with potassium iodoplatinate a brown-violet spot) and colour reactions: brown-violet with conc. sulfuric acid, changing to brown-green, red-violet with Erdmann reagent and yellow with conc. nitric acid.

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