ALKALOIDS OF *PAPAVER* GENUS XI.[1] ALKALOIDS OF *GLAUCIUM VITELLINUM*, POPULATION ISFAHAN

A. SHAFIEE[2], A. GHANBARPOUR, I. LALEZARI and S. LAJEVARDI[3]

Institute of Medicinal Plants, College of Pharmacy, Tehran University, Tehran, Iran

ABSTRACT.—*Glaucium vitellinum* Boiss and Buhse population Isfahan was shown to contain four major alkaloids, dicentrine (0.8%), bulbocapnine (0.4%), protopine (0.35%), salutaridine (0.2%), and twelve minor alkaloids, chelidonine, glaucine, corydine, isocorydine, *N*-methyllindcarpine, neolitsine, α-allocryptopine, *N*-methyllaurotetanine, dehydrodicentrine, dicentrinone, dihydrosanguinarine, dihydrochelerythrine. Neolitsine was found for the first time in *Papaveraceae*; dihydrosanguinarine and dihydrochelerythrine were detected for the first time in *Glaucium*. In addition, 4-hydroxybulbocapnine was also isolated and reported for the first time.

In a continuation of chemotaxonomic studies of Iranian wild species of the *Papaveraceae* family (1–10), the alkaloids of *Glaucium vitellinum* Boiss and Buhse population Isfahan[4] were studied. *Glaucium vitellinum* is a perennial plant scattered in Isfahan in the southern part of Iran at an altitude of about 1000 m. The plant blooms from the end of March until the end of July. The four petals are yellow with no spot on the base. The height of the plant is 45–90 cm.

EXPERIMENTAL[5]

PLANT MATERIAL.—The aerial parts of *Glaucium vitellinum* Boiss and Buhse collected in May, 1977, were air dried in the shade and then at 60° to a constant weight and powdered so that all the material could be passed through a mesh not larger than 0.5 mm.

EXTRACTION PROCEDURE.—To 1000 g of powdered plant material, 3 liters of methanol was added; the mixture was stirred over night at room temperature and filtered. The marc was washed with 2 liters of methanol. The extraction procedure was repeated three times. The combined methanol extract was evaporated under reduced pressure. To the residue was added 300 ml of acetic acid-water (50:50), and the mixture was filtered. The filtrate was extracted with petroleum ether (3 x 150 ml) to remove colored material. The aqueous layer was then made alkaline with 15% ammonia and extracted with chloroform (4 x 200 ml). Evaporation of the solvent gave a crude mixture of alkaloids (25 g).

COLUMN CHROMATOGRAPHY.—The crude extract (25 g) was dissolved in chloroform (50 ml) and placed on a chromatographic column (4.5 cm diameter) with 1000 g of alumina (neutral, activity II) as the absorbent.[6] The column was eluted consecutively with petroleum ether, 10% chloroform-petroleum ether, 20% chloroform-petroleum ether, 30% chloroform-petroleum ether, 40% chloroform-petroleum ether, 50% chloroform-petroleum ether, chloroform, 10% methanol-chloroform, and 20% methnol-chloroform. A quantity of 300 ml was collected for each fraction. The solvent was removed from each fraction under reduced pressure. The chromatography was monitored by tlc using three different solvent systems: A, ethyl acetate-methanol-ammonia (85:10:5); B, ether-methanol-ammonia (97:2:1) and C, petroleum ether-chloroform-diethyl amine (70:20:10).

---

[1]For paper X in the series, see reference 10. A preliminary account of this work was presented in the first joint meeting of the American Society of Pharmacognosy and the Phytochemical Society of North America, Oklahoma, U.S.A., August, 1978.

[2]To whom correspondence should be addressed.

[3]This work was a part of S. Lajevardi's dissertation for the degree of Pharmacy Doctorate.

[4]The plant was identified by Professor K. Hummel, Tubingen University; a herbarium sample was deposited in the Herbarium of the College of Pharmacy, Tehran University.

[5]Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer model 267 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT 311 spectrometer at 70 ev. Uv spectra were taken using a Varian model 635 spectrometer. Specific rotations were taken on a Perkin-Elmer model 241 polarimeter.

[6]Alumina and silica gel were obtained from Merck, Darmstadt, West Germany.

PREPARATIVE TLC.—Similar fractions obtained from chromatography were combined, and the solvent was removed under reduced pressure. The components of the residue were separated by preparative tlc using silica gel and one of the above solvent systems (See table 1).

TABLE 1. *Chromatographic results.*

Alkaloids	Solvent[a] for column elution (%)	Tlc (R_f)[b]		
		A	B	C
Dihydrochelerythrine	10	0.83	0.93	0.57
Dihydrosanguinarine	10	0.86	0.89	0.59
Dehydrodicentrine	10	0.8	0.55	0.55
Dicentrine	20	0.65	0.25	0.42
Neolitsine	20	0.71	0.45	0.42
Glaucine	20	0.61	0.18	0.54
N-Methyllindcarpine	30	0.58	0.15	0.42
Bulbocapnine	30	0.65	0.36	0.31
4-Hydroxybulbocapnine	30	0.55	0.18	0.13
(±)-Chelidonine	40	0.8	0.5	0.48
N-Methyllaurotetanine	40	0.59	0.19	0.52
α-Allocryptopine	40	0.58	0.14	0.47
Protopine	40	0.77	0.38	0.49
Isocorydine	50	0.73	0.17	0.36
Corydine	50	0.68	0.18	0.32
Salutaridine	100	0.42	0.04	0.15
O-Methylflavinantine	100	0.35	0.01	0.15
Dicentrinone	100	0.3	—	0.06

[a]Chloroform-petroleum ether.
[b]Solvent system for tlc: A, ethyl acetate-methanol-ammonia (85:10:5); B, ether-methanol-ammonia (97:2:1); C, petroleum ether-chloroform-diethyl amine (70:20:10).

RESULTS

The following alkaloids were isolated from *Glaucium vitellinum* population Isfahan.

DIHYDROCHELERYTHRINE, DIHYDROSANGUINARINE AND DEHYDRODICENTRINE.—Combined fractions which were eluted with 10% chloroform-petroleum ether showed three spots on tlc. They were separated by preparative tlc (silica gel, solvent system B). The fastest moving fraction (R_f 0.93) was crystallized from ethanol to give dihydrochelerythrine: mp 163–166° [lit. (11) mp 165–166°]; uv λ max (ethanol) 279 nm; nmr ($CDCl_3$): 7.86–6.86 (m, 6H, aromatic), 6.04 (s, 2H, OCH_2O), 4.30 (s, 2H, CH_2N), 3.93 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3) and 2.62 ppm (s, 3H, NCH_3).

Mp and mmp as well as uv and ir spectral data were identical with an authentic sample.[7]

The next fraction (solvent system B, R_f 0.89) was crystallized from ethanol to give dihydrosanguinarine: mp 190–192° [lit. (12) mp 192°]; uv λ max (methanol) 283 (log ε 4.61), 323 nm (log ε 4.26); nmr ($CDCl_3$): 7.66–6.79 (m, 6H, aromatic), 6.04 (s, 4H, OCH_2O), 4.16 (s, 2H, CH_2N) and 2.58 ppm (s, 3H, NCH_3). The mp, ir and uv spectral data were identical with those reported (12).

The next fraction (R_f 0.55) was crystallized from ethanol to give dehydrodicentrine: mp 216–218 [lit. (10) mp 216–218].

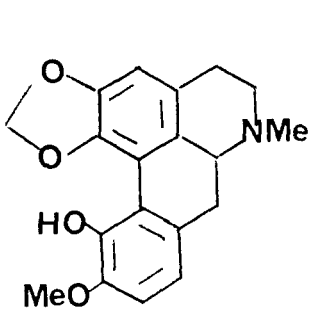
[7]An authentic sample of dihydrochelerythrine was provided kindly by Dr. V. Preininger of Palacky University, Olomuc, Czechoslovakia.

DICENTRINE, NEOLISTINE AND GLAUCINE.—Combined fractions which were eluted with 20% chloroform-petroleum ether showed three spots on tlc. They were separated by preparative tlc (silica gel, solvent system B). The fastest moving fraction [R_f 0.45] was crystallized from acetone to give neolitsine: mp 149–150° [lit. (13), mp 149–150]; uv λ max (methanol) 283 (log ε 4.01), 312 nm (log ε 4.20); nmr ($CDCl_3$): 7.57 (s, 1H, H_{11}), 6.68 (s, 1H, H_8), 6.43 (s, 1H, H_3), 5.96 (d, 1H, OCHO), 5.93 (s, 2H, OCH_2O), 5.83 (d, 1H, OCHO) and 2.47 ppm (s, 3H, NCH_3); mass spectrum *m/e* 323 (M^+), 322, 319, 292, 280, 163, 161, 103, 102, 85, 82, 71, 57. The uv and ir spectral data were identical with those reported (14, 15).

The next fraction (R_f 0.25) was crystallized from ethanol to give dicentrine (0.8%): mp 166–169 [lit. (5) mp 166–169].

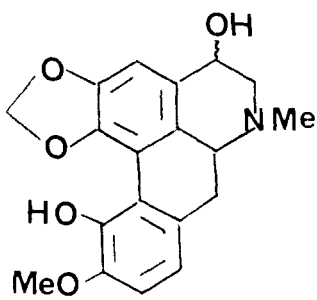
The next fraction (R_f 0.18) gave a crystalline compound which was identified as glaucine: mp 116–118 [lit. (17) mp 120–121, lit. (10) mp 116–118].

N-METHYLLINDCARPINE, BULBOCAPNINE AND 4-HYDROXYBULBOCAPNINE.—Combined fractions which were eluted with 30% chloroform-petroleum ether showed three spots on tlc (silica gel, solvent system C). They were separated by preparative tlc (silica gel, solvent system C). The fastest moving fraction [R_f 0.42] was crystallized from ethanol to give *N*-methyllindcarpine: mp 198–200° [lit. (9) mp 198–200°].



I

Bulbocapnine



II

4-Hydroxybulbocapnine

Figure I

The next fraction [R_f 0.31] was crystallized from ethanol to give bulbocapnine (I) (0.4%): mp 199–200° [lit. (6) mp 199–200°]; uv λ max (methanol) 269 (log ε 4.15), 282 sh (log ε 4.12), 305 nm (log ε 3.75); $[\alpha]^{20}D$ +232 ($CHCl_3$); nmr ($CDCl_3$): 6.83 (s, 2H, $H_{8,9}$), 6.64 (s, 1H, H_3), 6.10 (d, 1H, OCHO), 5.95 (d, 1H, OCHO), 3.92 (s, 3H, OCH_3) and 2.57 (s, 3H, NCH_3).

The next fraction was crystallized from chloroform to give a compound (R_f 0.13): mp 231–233°; [α]D +100° [0.14, $CHCl_3$]; uv λ max (methanol)270 (log ε 4.10), 280 sh (log ε 4.05), 303 nm (log ε 3.71); nmr ($CDCl_3$): 6.93 (s, 1H, H_3), 6.83 (s, 2H, H_8, H_9), 6.13 (d, 1H, OCHO), 5.95 (d, 1H, OCHO), 5.15 (broad s, 2H, OH), 4.50 (unresolved t, 1H, H_4), 3.93 (s, 3H, OCH_3) and 2.56 ppm (s, 3H, NCH_3); mass spectrum *m/e* (%) 341 (M^+, 89), 340 (34), 326 (54), 324 (11), 308 (13), 299 (19), 298 (100), 296 (15), 283 (19), 269 (30), 139 (14), 85 (12), 83 (17), 71 (10), 42 (15).

Anal. Calcd. for $C_{19}H_{19}NO_5$: C, 66.86; H, 5.57; N, 4.11. Found: C, 66.98; H, 5.39; N, 4.30.

The uv of this alkaloid was similar to bulbocapnine. The nmr spectrum was also very similar to bulbocapnine, the only difference was that the H_3 shifted 17.4 Hz downfield relative to H_3 in bulbocapnine. A similar downfield shift (18 Hz) was observed in steporphine (4-hydroxyromerine) relative to roemerine (16) and in cataline (4-hydroxyglaucine) relative to glaucine (16). Thus, we concluded that this alkaloid is most probably 4-hydroxybulbocapnine (II). The mass spectrum was also in accordance with the suggested structure and was similar to cataline and steporphine (16).

(±)-CHELIDONINE, PROTOPINE, N-METHYLLAUROTETANINE AND α-ALLOCRYPTOPINE.—Combined fractions which were eluted with 40% chloroform-petroleum ether showed four spots on tlc. They were separated by preparative tlc (silica gel, solvent system B). The fastest moving fraction (R_f 0.50) was separated and crystallized from ethanol to give (±)-chelidonine: mp 218–220° [lit. (10), mp 218–220°].

The next fraction (R_f 0.38) was crystallized from ethanol to give protopine (0.35%): mp 205–207° [lit. (18) 207].

The next fraction (R_f 0.19) was an oil which was crystallized as the hydrobromide and was identified as *N*-methyllaurotetanine: mp 237–238° [lit. (19) mp 237–238°].

The next fraction (R_f 0.14) was crystallized from ethanol to give α-allocryptopine: mp 160° [lit. (20), mp 160–161°].

ISOCORYDINE.—The first four fractions which were eluted with 50% chloroform petroleum ether contained almost pure isocorydine which was further purified by tlc on silica gel using solvent system B (R_f 0.17): mp 185–186° (ethanol) [lit. (21), mp 185°].

CORYDINE.—Fractions six to nine which were eluted with 50% chloroform-petroleum ether contained mainly corydine which was further purified by preparative tlc using solvent system A [R_f 0.68]: mp 148° (ethanol) [lit. (22), mp 148°].

SALUTARIDINE, O-METHYLFLAVINANTINE AND DICENTRINONE.—Combined fractions which were eluted with chloroform showed three spots on tlc. They were separated by preparative tlc (silica gel, solvent system A). The fastest moving fraction (R_f 0.42) was crystallized from ethanol to give salutaridine (0.2%): mp 197–199 [lit. (5), mp 197–199].

The next fraction (R_f 0.35) gave an oil which was crystallized as hydrochloride and was identified as *O*-methylflavinantine, mp 195–196° (ethanol) [lit. (7), mp 195–196].

The next fraction (R_f 0.3) was crystallized from chloroform to give dicentrinone, mp 299 [lit. (10), mp 299].

All the above alkaloids except dihydrosanguinarine, dihydrochelerythrine, neolistine and 4-hydroxybulbocapnine were previously reported by this laboratory (5–7, 9, 10) and their physical data were used for identification.

A literature survey (15, 23–24) revealed that neolitsine has not been previously found in *Papaveraceae*, and dihydrosanguinarine and dihydrochelerythrine have not been previously detected in the genus *Glaucium*. The presence of 4-hydroxybulbocapnine is reported for the first time.

ACKNOWLEDGMENTS

This work was supported by grant No. 600-1-37/1 from the Ministry of Sciences and Higher Education Research Development Council and International Science Foundation Grant No. 13. We are grateful to Dr. V. Preininger for a sample of dihydrochelerythrine.

Received 7 September 1978.

LITERATURE CITED

1. N. SHARGHI and I. LALEZARI, *Nature*, *213*, 1244 (1967).
2. I. LALEZARI, A. SHAFIEE and P. NASSERI-NOURI, *J. Pharm. Sci.*, **62**, 1718 (1973).
3. I. LALEZARI, P. NASSERI and R. ASGHARIAN, *J. Pharm. Sci.*, **63**, 1331 (1974).
4. A. SHAFIEE, I. LALEZARI, P. NASSERI-NOURI and R. ASGHARIAN, *J. Pharm. Sci.*, **64**, 1570 (1975).
5. I. LALEZARI, A. SHAFIEE and M. MAHJOUR, *J. Pharm. Sci.*, **65**, 923 (1976).
6. A. SHAFIEE, I. LALEZARI and M. MAHJOUR, *J. Pharm. Sci.*, **66**, 593 (1977).
7. A. SHAFIEE, I. LALEZARI, S. LAJEVARDI and F. KHALAFI, *J. Pharm. Sci.*, **66**, 873 (1977).
8. A. SHAFIEE, I. LALEZARI, F. ASSADI and F. KHALAFI, *J. Pharm. Sci.*, **66**, 1050 (1977).
9. A. SHAFIEE, I. LALEZARI and O. RAHIMI, *Lloydia*, **40**, 352 (1977).
10. A. GHANBARPOUR, A. SHAFIEE and M. PARCHAMI, *Lloydia*, **41**, 472 (1978).
11. K. YAMAGUCHI, "Spectral data of natural products", Elsevier publishing Co., London, **1970**, I, p. 554.
12. J. HOLUBEK and O. STROUF, "Spectral data and physical constants of alkaloids", Heyden & Son, London, 1965, I, p. 97.
13. W. H. HUI, S. N. LOO and H. R. ARTHUR, *J. Chem. Soc.*, **1965**, 2285 (1965).
14. J. HOLUBEK and O. STROUF, "Spectral data and physical constants of alkaloids", Heyden & Son, London, 1965, IV, p. 564.
15. H. GUINAUDEAU, M. LEBOEUF and A. CAVE, *Lloydia*, **38**, 293 (1975).
16. H. GUINAUDEAU, M. LEBOEUF and A. CAVE, *ibid.*, **38**, 312, 277, 290 (1975).
17. M. SHAMMA and B. S. DUDOCK, *J. Pharm. Sci.* **57**, 262 (1968).
18. W. H. PERKIN, *J. Chem. Soc.* **109**, 1023 (1916).
19. R. H. F. MANSKE and K. H. SHIN, *Can. J. Chem.*, **43**, 2180 (1965).
20. L. SLAVIKOVA and J. SLAVIK. 1955. Alkaloids of *papaveraceae.* VII. *Argemone mexicana. Chem. Listy*, **49**, 1546 (1955). *Chem. Abstr.*, **50**, 4990h.
21. A. RUEGGER, *Helv. Chim. Acta*, **42**, 754 (1959).
22. D. S. BHAKUNI, S. TEWARI and M. H. DHAR, *Phytochemistry*, **11**, 1819 (1972).
23. F. SANTAVY, 1970. In Manske (ed), "The alkaloids", Academic press, New York, 1970, **12**, 337.
24. J. J. WILLAMAN and L. HUI-LIN, *Lloydia supplement*, **33**, No. 3A, 158 (1970).