THE PROTOPINE ALKALOIDS

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Sixteen naturally occurring protopines are known. The prototype for these bases is the widely distributed alkaloid protopine (**1**) whose numbering system is indicated in expression **1**. The listing for the occurrence of this alkaloid as well as of allocryptopine (**2**) emphasizes the more recent findings. For an older listing of the occurrence of protopine (**1**) and allocryptopine (**2**) in plants, the reader should refer to H.-G. Boit's *Ergebnisse der Alkaloid-Chemie Bis 1960*, Akademie Verlag, Berlin (1961), pp. 349–351.

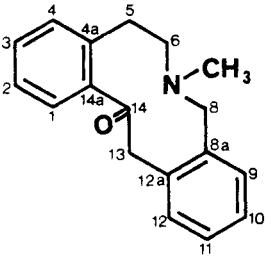
Protopines are optically inactive, except in the case of C–13 substitution. The absolute configuration of the 13-methylated base corycavine (**13**) has been recently determined by correlation with a 13-methylated berbine of established absolute configuration (37).

The alkaloid oreophiline is not a protopine base as long believed, but is instead a berbine (81).

Among the Rutaceae, the genera *Fagara* and *Zanthoxylum* are generally considered to be identical. Neverthless, in the present listing, they have been kept apart to reflect the botanical names cited in the literature. It will be noted also that pseudoprotopine (**9**) and fagarine II (**10**) are the only two protopines substituted at C–10,11 rather than at the more common C–9,10 sites. Significantly, both of these alkaloids are found only among the Rutaceae.

Uv wave lengths are in nm, and ir frequencies in cm^{-1}. The solvent is always given whenever it has been indicated in the original literature.

^1H nmr chemical shifts are in $CDCl_3$ solution unless indicated otherwise. In instances where chemical shift assignments were changed from those made in the original literature, this has been indicated with a double asterisk (**) as a superscript immediately after the appropriate reference. The H–1 absorption in the protopines is found further downfield than that due to H–4 because of deshielding by the carbonyl function (5). The C–5 methylene protons are found near δ2.6



and the C–6 protons further downfield near δ2.8 (72). Whenever a methylenedioxy group is present at C–9,10, the H–11 and 12 protons appear as a singlet when $CDCl_3$ is the solvent, and as a doublet of doublets if a little C_6D_6 is added (39). Changes in the nmr spectra of coulteropine (**11**) and other protopine alkaloids in varying

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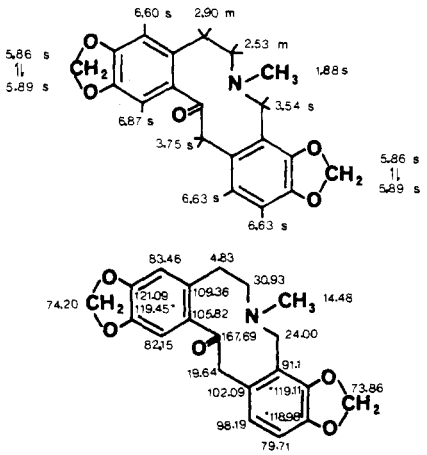
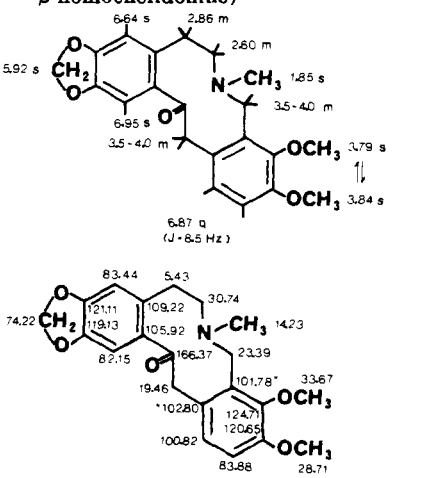
concentrations of TFA in $CDCl_3$ have been noted (112). ^{13}C nmr spectra are in 5% C_6D_6 in $CDCl_3$. ^{13}C nmr chemical shift values with identical superscripts are interchangeable. ^{13}C nmr values obtained in TFA-*d* are quite different from the values given below, specifically because protonation results in quinolizidinium salt formation. Typically, in TFA-*d*, C–5 appears at 25 ppm, C–6 at 56 ppm, C–8 at 59 ppm, C–13 at 41 ppm and C–14 at 95 ppm, while the N-methyl carbon is near 46 ppm (131).

1. PROTOPINE



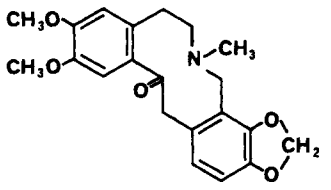
$C_{20}H_{19}O_5N$: 353.12629
MP: 207–208° (MeOH) (42)
UV: (EtOH) 238 sh (3.68), 288 (3.60) (118)
IR: (KBr) 1670, 935 (76)
^1H NMR: (100 MHz) (39)
^{13}C NMR: (73)
MS: 353 (M^+), 338, 336, 325, 322, 310, 309, 295, 281, 267, 252, 251, 205, 190, 163, 148 (base), 134 (15)
SOURCES: BERBERIDACEAE: *Berberis* (16)
FUMARIACEAE: *Corydalis* (30, 33, 34, 38, 40, 42, 43, 44, 49, 50, 51, 54, 55, 58, 59, 60, 64, 65, 66, 67, 76, 86, 88, 91, 118, 119, 120, 121) *Dactylicapnos* (61) *Dicentra* (38, 52, 56) *Fumaria* (1, 29, 47, 57, 68, 69)
PAPAVERACEAE: *Argemone* (2, 25, 26, 114, 115, 116) *Bocconia* (103, 122) *Chelidonium* (36, 94) *Eschscholtzia* (102) *Glaucium* (21, 84, 95, 96, 97, 98, 127, 128) *Hunnemannia* (63, 108) *Hylomecon* (99) *Macleaya* (45) *Meconella* (111) *Meconopsis* (105, 106) *Papaver* (4, 6, 7, 11, 18, 32, 71, 75, 77, 79, 80, 81, 83, 84, 85, 87, 89, 90, 100, 104) *Roemeria* (107) *Romneya* (110) *Sanguinaria* (99) *Stylomecon* (99)
SAPINDACEAE: *Pteridophyllum* (31, 46)

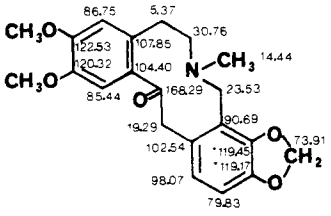
2. ALLOCRYPTOPINE
(α-Fagarine, γ-homochelidonine, β-homochelidonine)



$C_{20}H_{19}O_5N$: 369.15759
MP: α-160–161° (EtOH-ether) (108)
β-164–165° (acetone) (123)
UV: (EtOH) 230 (4.1), 285 (3.8) (108)
IR: (Nujol) 1652, 1042, 940 (51)
^1H NMR: (13)**
^{13}C NMR: (73)
MS: 369 (M^+), 354, 352, 341, 338, 326, 325, 311, 297, 283, 268, 267, 206, 164 (base), 163, 149, 134 (15)
SOURCES: FUMARIACEAE: *Corydalis* (33, 51, 54, 58, 67, 119, 120, 121), *Dactylicapnos* (61)
PAPAVERACEAE: *Argemone* (2, 25, 26, 113, 115, 116) *Bocconia* (103, 122) *Eschscholtzia* (102) *Glaucium* (21, 84, 95, 98, 101, 127, 128) *Hunnemannia* (63, 108) *Hylomecon* (99) *Macleaya* (45) *Meconopsis* (106) *Papaver* (6, 28, 71, 83, 84, 100) *Sanguinaria* (99) *Stylomecon* (99)
RANUNCULACEAE: *Thalictrum* (124, 125, 130)
RUTACEAE: *Fagara* (3, 93) *Zanthoxylum* (10, 39)
SAPINDACEAE: *Pteridophyllum* (31, 46)

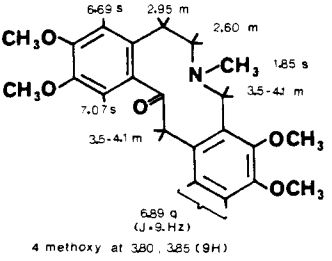
3. CRYPTOPINE
(Thalisopyrine, cryptocavine)[2]

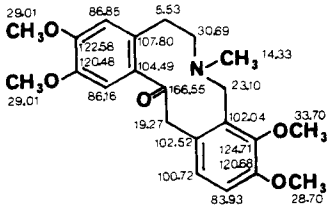




$C_{21}H_{23}O_5N$: 369.15759
MP: 222–223° ($CHCl_3$-EtOH) (99)
UV: (MeOH) 234 (4.20), 286 (3.95) (99)
^{13}C NMR: (73)
MS: 369 (M^+), 354, 352, 341, 338, 326, 325, 311, 297, 283, 268, 267, 221, 190, 179, 148 (base) (15)
SOURCES: FUMARIACEAE: *Corydalis* (53, 55, 60), *Dicentra* (52)
PAPAVERACEAE: *Argemone* (26, 113) *Meconopsis* (105, 106) *Papaver* (4, 6, 18, 71, 75, 77, 82, 83, 84) *Stylomecon* (99)
RANUNCULACEAE: *Thalictrum* (35, 92)

4. MURAMINE
(Cryptopalmatine)

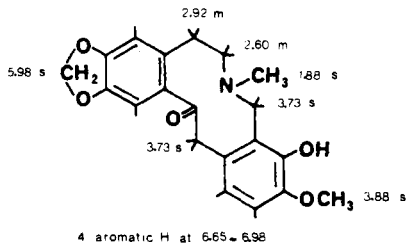


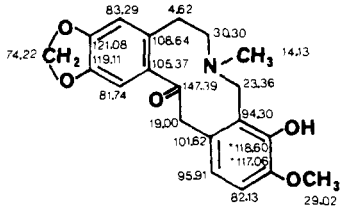


$C_{22}H_{27}O_5N$: 385.18889
MP: 174–176° (acetone) (97)
^1H NMR: (13)**
^{13}C NMR: (73)
MS: 385 (M^+), 327, 299, 283, 206, 179, 164 (base), 149, 121 (13)
SOURCES: PAPAVERACEAE: *Argemone* (109, 114, 115) *Glaucium* (97) *Papaver* (7, 13, 22, 70, 71, 75, 89, 90)

[2]The alkaloid cryptocavine was tentatively assumed to be isomeric with cryptopine, and to incorporate a carbonyl at C-13 rather than at C-14 (62, 59, 58). In all probability, however, cryptocavine is identical with cryptopine.

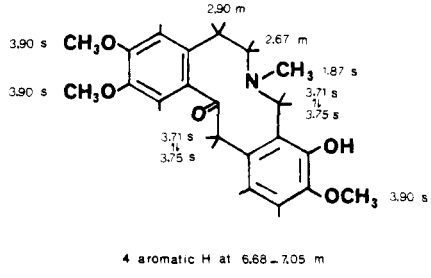
5. HUNNEMANINE





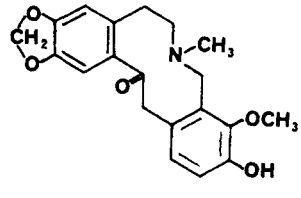
$C_{20}H_{21}O_5N$: 355.14194
MP: 208–209° ($CHCl_3$-EtOH) (108)
UV: (EtOH) 233 (4.11), 285 (3.92) (23)
IR: ($CHCl_3$) 3510, 1650 (23)
^1H NMR: (23)
^{13}C NMR: (73)
MS: 355 (M^+), 340, 338, 327, 324, 312, 311, 297, 283, 269, 254, 253, 206 (base), 192, 163, 150, 135, 134 (15)
SOURCES: PAPAVERACEAE: *Argemone* (113) *Hunnemannia* (108, 63)

6. PROTOTHALIPINE



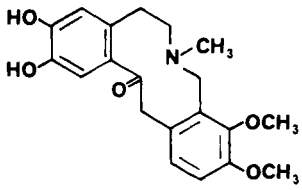
$C_{21}H_{25}O_5N$: 371.17325
MP: 195–196° (decomp.) (MeOH) (129)
UV: (MeOH) 232 (4.60), 282 (3.91) (129)
IR: ($CHCl_3$) 3540, 1655 (129)
^1H NMR: (129)
MS: 371 (M^+), 269, 223, 222 (base), 193, 192, 191, 179, 178, 165, 164, 151, 150, 135, 121, 107, 77, 63, 59, 57, 55, 53, 51 (129)
SOURCES: RANUNCULACEAE: *Thalictrum* (129)

7. THALICTRICINE
(Thalictrisine)



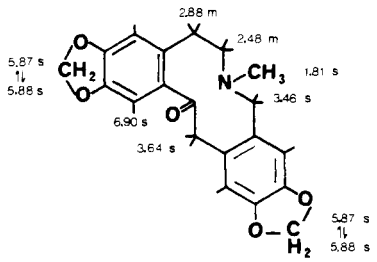
$C_{20}H_{21}O_5N$: 355.14194
MP: 261–263° (MeOH) (123)
UV: 288 (3.95) (123)
IR: 3640, 2900, 2860, 1640, 1615, 1580, 1505, 1240, 1130, 1040, 930 (123)
MS: 355 (M^+), 269, 207, 206 (base), 192, 150 (123)
SOURCES: RANUNCULACEAE: *Thalictrum* (123, 124, 125)

8. VAILLANTINE[3]



$C_{20}H_{23}O_5N$: 357.15759
MP: 165–167° (29)
UV: 292 (3.92) (29)
IR: (KBr) 1650, 1600 (29)
MS: 357 (M^+), 164 (base) (29)
SOURCES: FUMARIACEAE: *Fumaria* (29)

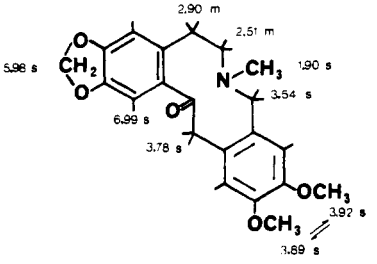
9. PSEUDOPROTOPINE



3 aromatic H at 6.58 (2H), 6.67

$C_{20}H_{19}O_5N$: 353.12629
MP: 200–202° (MeOH) (39)
UV: (EtOH) 291 (3.99) (39)
^{1}H NMR: (100 MHz) (39)
MS: 353 (M^+), 148 (base) (39)
SOURCES: RUTACEAE: *Zanthoxylum* (39)

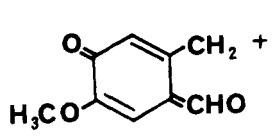
10. FAGARINE II[4]



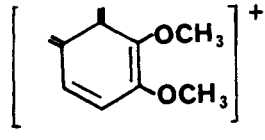
3 aromatic H at 6.67, 6.70, 6.80

$C_{21}H_{23}O_5N$: 369.15759
MP: 200–201° (EtOH) (24)
UV: (EtOH) 232 (4.06), 286 (3.91) (24)
IR: (Nujol) (12)
^{1}H NMR: (78)
SOURCES: RUTACEAE: *Fagara* (3, 12, 14, 117)

[3]This structural assignment may be in error since a catechol system would not have survived the conditions of isolation. The base peak, m/e 164 could actually correspond to ion *A* rather than to *B* as claimed. It follows that in vaillantine one phenolic group is probably attached to the top ring, and the other to the bottom ring.



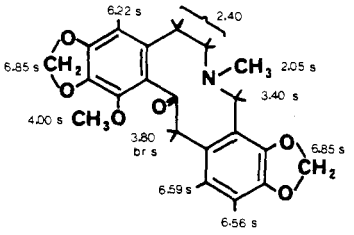
A



B

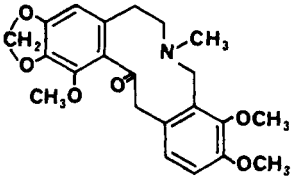
[4]The structural isomer of fagarine II, with methoxyl groups at C-2 and 3, and a methylenedioxy at C-10,11 has been synthesized (78).

11. COULTEROPINE



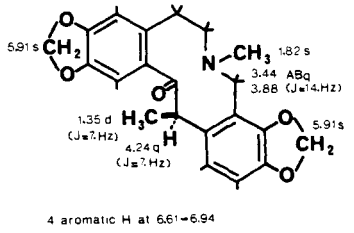
$C_{21}H_{21}O_6N$: 383.13685
MP: 167–168° (MeOH) (110)
UV: (EtOH) 286 (3.85) (110)
IR: ($CHCl_3$) 1675 (110)
^1H NMR[5]: (110)
MS: 383 (M^+), 193, 170, 148 (base) (110)
X-RAY: HBr salt (112)
SOURCES: PAPAVERACEAE: *Romneya* (110)

12. 1-METHOXYALLOCRYPTOPINE



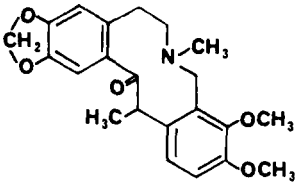
$C_{22}H_{25}O_6N$: 399.16815
MP: 125–129° (MeOH) (126)
UV: 283 (3.60) (126)
IR: 1680 (126)
MS: 399 (M^+), 383, 368, 355, 341, 325, 313, 297, 282, 232, 220, 206, 193, 164 (base), 149 (126)
SOURCES: Synthesis (126)

13. CORYCAVINE
(Corycavamine)[6]



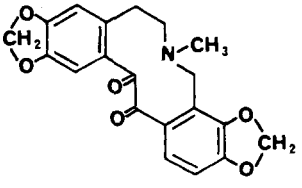
$C_{21}H_{21}O_5N$: 367.14194
MP: 221–222° (MeOH) (42)
$[\alpha]^{20}D$: 167° (c=2.2 $CHCl_3$) (20)
UV: (MeOH) 291 (3.86) (76)
IR: (KBr) 1660, 935 (76)
^1H NMR: (76)
MS: 367 (M^+), 206, 204, 163, 162 (42)
SOURCES: FUMARIACEAE: *Corydalis* (20, 42, 67, 76)

14. CORYCAVIDINE



$C_{22}H_{25}O_5N$: 383.17324
MP: 212–213° (EtOH) (19)
$[\alpha]D$ +203° (c=1 $CHCl_3$) (19)
SOURCES: FUMARIACEAE: *Corydalis* (19, 9)

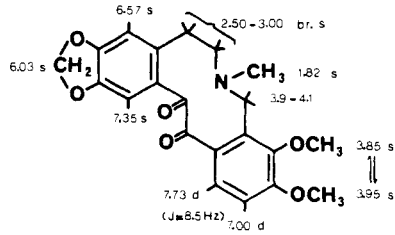
15. 13-OXOPROTOPINE
(13-Oxyprotopine)



$C_{20}H_{17}O_6N$: 367.10555
MP: 226–230° (acetone) (27)
UV: (EtOH) 288 (3.97), 317 (3.93) (48)
IR: ($CHCl_3$) 1680, 1668 (48)
MS: 367 (M^+), 204, 190, 162 (base), 134 (27)
SOURCES: PAPAVERACEAE: *Papaver* (87)

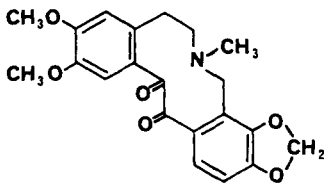
[5]Some of the chemical shifts indicated here were culled from a photographic reproduction of the spectrum.
[6]Corycavine and corycavamine are identical (9).

16. 13-OXOALLOCRYPTOPINE



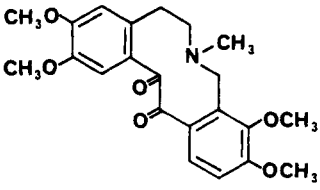
$C_{21}H_{21}O_6N$: 383.13685
MP: 207–209° (acetone) (27)
IR: ($CHCl_3$) 1680–1660 (74)
^1H NMR: (74)
MS: 383 (M^+), 220, 206, 178 (base), 150 (27)
SOURCES: Synthesis (27)

17. 13-OXOCRYPTOPINE
(13-Oxycryptopine)



$C_{21}H_{21}O_6N$: 383.13685
MP: 185–186° (acetone) (27)
MS: 383 (M^+), 204, 190, 162 (base), 134 (27)
SOURCES: PAPAVERACEAE: *Papaver* (8)

18. 13-OXOMURAMINE
(Alpinone)



$C_{22}H_{23}O_6N$: 399.16815
MP: 173–180° (acetone) (27)
UV: (MeOH) 231 (4.35), 287 (4.30), 306 sh (4.10) (17)
IR: (KBr) 1675, 1660 (17)
MS: 399 (M^+), 220, 206, 178 (base), 150 (27)
SOURCES: PAPAVERACEAE: *Papaver* (17, 71)

Alphabetical List of the Protopines

Molecular Weights and Molecular Compositions

353.12629 $C_{20}H_{19}O_5N$
Protopine (1)
Pseudoprotopine (9)
355.14194 $C_{20}H_{21}O_5N$
Hunnemanine (5)
Thalictricine (7)
357.15759 $C_{20}H_{23}O_5N$
Vaillantine (8)
367.10555 $C_{20}H_{17}O_6N$
13-Oxoprotopine (15)
367.14194 $C_{21}H_{21}O_5N$
Corycavine (13)
369.15759 $C_{21}H_{23}O_5N$
Allocryptopine (2)
Cryptopine (3)
Fagarine II (10)
371.17325 $C_{21}H_{25}O_5N$
Protothalipine (6)
383.13685 $C_{21}H_{21}O_6N$
Coulteropine (11)
13-Oxoallocryptopine (16)
13-Oxocryptopine (17)
383.17324 $C_{22}H_{25}O_5N$
Corycavidine (14)
385.18889 $C_{22}H_{27}O_5N$
Muramine (4)
399.16815 $C_{22}H_{25}O_6N$
13-Oxomuramine (18)
1-Methoxyallocryptopine (12)

Botanical Occurrence of the Protopines

BERBERIDACEAE
Berberis
Protopine (1)
FUMARIACEAE
Corydalis
Protopine (1)
Allocryptopine (2)
Cryptopine (3)
Corycavine (13)
Corycavidine (14)
Dactylicapnos
Protopine (1)
Allocryptopine (2)
Dicentra
Protopine (1)
Cryptopine (3)
Fumaria
Protopine (1)
Vaillantine (8)
PAPAVERACEAE
Argemone
Protopine (1)
Allocryptopine (2)
Cryptopine (3)
Muramine (4)
Hunnemanine (5)
Bocconia
Protopine (1)
Allocryptopine (2)
Chelidonium
Protopine (1)
Eschscholtzia
Protopine (1)
Allocryptopine (2)
Glaucium
Protopine (1)
Allocryptopine (2)
Muramine (4)
Hunnemannia
Protopine (1)
Allocryptopine (2)
Hunnemanine (5)
Hylomecon
Protopine (1)
Allocryptopine (2)
Macleaya
Protopine (1)
Allocryptopine (2)
Meconella
Protopine (1)
Meconopsis
Protopine (1)
Allocryptopine (2)
Cryptopine (3)
Papaver
Protopine (1)
Allocryptopine (2)
Cryptopine (3)
Muramine (4)
13-Oxoprotopine (15)
13-Oxocryptopine (17)
13-Oxomuramine (18)
Roemeria
Protopine (1)
Romneya
Protopine (1)
Coulteropine (11)
Sanguinaria
Protopine (1)
Allocryptopine (2)
Stylomecon
Protopine (1)
Allocryptopine (2)
Cryptopine (3)
RANUNCULACEAE
Thalictrum
Allocryptopine (2)
Cryptopine (3)
Protothalipine (6)
Thalictricine (7)
RUTACEAE
Fagara
Allocryptopine (2)
Fagarine II (10)
Zanthoxylum
Allocryptopine (2)
Pseudoprotopine (9)
SAPINDACEAE
Pteridophyllum
Protopine (1)
Allocryptopine (2)

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