

THE ARISTOLOCHIC ACIDS AND ARISTOLACTAMS

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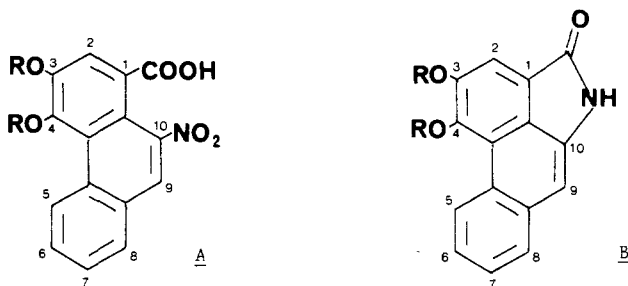
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Fourteen aristolochic acids are known, two of which have been isolated as the methyl esters. Aristolochic acids are often accompanied by aristolactams, twelve of whom have been obtained from natural sources.

Aristolochic acids have been found only among the Aristolochiaceae, as well as in butterflies that feed on such plants. The botanical range of the aristolactams is somewhat broader. Most of them are still found in the Aristolochiaceae, although there are also well authenticated reports of their occurrence in some members of the Annonaceae, Menispermaceae and Monimiaceae.

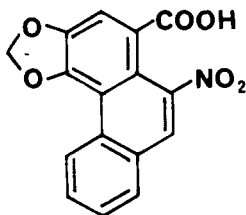
A singular structural feature of the aristolochic acids as well as the aristolactams has been that whenever an oxygenated function was present in the bottom aromatic ring, this substituent was situated at either C-6 or C-8. Similarly, when two substituents were present, these could be found only at C-6 and C-8. Very recently, however, 7-hydroxy- (6) and 7-methoxyaristolochic acid-A (9) have been reported which are oxygenated at both C-7 and C-8. Another unusual species is debilic acid (11), which is strictly speaking a homoaristolochic acid since it incorporates a carboxymethyl sidechain at C-1.

Even though aristolochic acids and aristolactams are non-basic, they are nevertheless classified as aporphinoids since their respective skeletons **A** and **B** bear a distinct similarity to that of the aporphines.



The chemistry, biogenesis and pharmacology of the aristolochic acids and aristolactams has been reviewed.² Uv wavelengths are in nm, ir frequencies in cm^{-1} , and nmr chemical shifts in ppm on the δ scale. Melting points are in degrees centigrade.

1. ARISTOLOCHIC ACID-II

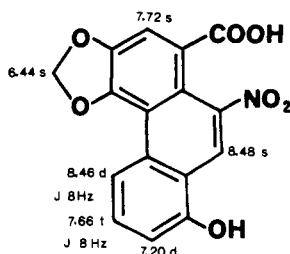


$\text{C}_{16}\text{H}_9\text{O}_6\text{N}$: 311.2502
(Me ester): 325.2770
MP: 269-271° dec. (66)
UV: 251 (4.51), 297 (4.15), 353 (3.65) (48)
IR: (Me ester) KBr 1718, 1515, 1548 (36)
MS: (Me ester) 325, 294, 279 (100), 264, 250, 236, 208, 150 (47)
SOURCES: ARISTOLOCHACEAE: *Aristolochia argentina* (51), *clematitis* (23, 47, 48, 52), *debilis* (45, 69), *esperanzae* (51), *longa* (61), *manshuriensis* (54), *rotunda* (5), *sipho* (syn. *durior*) (12)

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*M. Shamma and J. L. Moniot, "Isoquinoline Alkaloids Research 1972-1977" Plenum Press, New York (1978), pp. 189-196.

2. ARISTOLOCHIC ACID-Ia

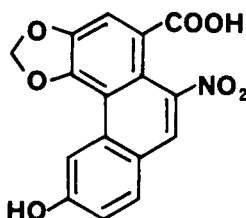
C₁₆H₉O₇N: 327.2496

MP: 278° (72)

UV: (EtOH) 221, 255, 283, 312, 389 (72)

NMR: (DMSO-d₆) (72)

MS: 327, 293, 281, 279, 253, 241, 225, 195, 179, 167, 139 (53)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia chilensis* (72). Aristolochic acid-Ia has also been found in the butterfly *Zerynthia polyxena* (53, 72).3. ARISTOLOCHIC ACID-C
(Aristolochic acid-IIIa)C₁₆H₉O₇N: 327.2496

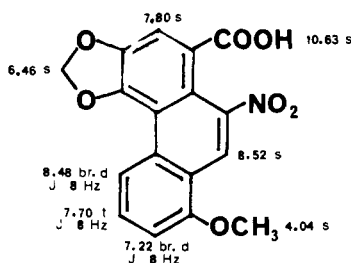
(Me ester): 341.2764

MP: 280° dec. (EtOH) (57)

(Me ester) 272-275° (EtOH-acetone) (57)

IR: (Nujol) 3460, 1681, 1508, 1328 (66)

MS: 327 (100), 312, 309, 297, 293, 282, 281, 279, 269, 225, 195, 179, 167, 150, 139 (53)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia debilis* (9, 20, 47, 57, 67), *fangchi* (66), *rotunda* (5), *watsonii* (53). Aristolochic acid-C has also been found in the butterfly *Zerinthia polyxena* (53).4. ARISTOLOCHIC ACID-I¹
(Aristolochic acid-A)
(Aristolochic acid)C₁₇H₁₁O₇N: 341.2764

(Me ester): 355.3032

MP: 275-278° (DMF-EtOH) (34)

280° dec. (EtOH) (13)

283-285° (MeOH-CHCl₃) (52)

UV: (EtOH) 221 (4.47), 250 (4.51), 317 (4.05), 390 (3.78) (51)

IR: (KBr) 1695, 1515, 1340, 1266, 1036, 942 (51)

NMR: (DMSO-d₆) (34)

MS: 341 (35), 296 (36), 295 (100), 75 (52), 74 (36), 69 (31), 63 (35), 53 (36) (22)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia acuminata* (43), *argentina* (51, 56), *badamae* (60), *baetica* (6), *bracteata* (26, 27, 42, 58), *chilensis* (72), *clematidis* (5, 9, 20, 21, 23, 47, 48, 50, 52, 59, 60), *debilis* (29, 65, 69, 71), *elegans* (60), *esperanzae* (51), *fangchi* (10, 62, 66), *fimbriata* (60), *graffithii* (64), *indica* (14, 15, 18, 33, 34, 49, 63), *kaempferi* (65), *kwangsiensis* (11, 39), *longa* (15, 21, 61), *manshuriensis* (44, 54), *maurorum* (28), *maxima* (21), *mollissima* (17, 24), *multiflora* (43), *ornithocephala* (60), *pandurata* (21), *reticulata* (14, 15), *rotunda* (5, 20, 60), *serpentaria* (15, 18, 21), *sipho* (syn. *durior*) (12, 13, 21, 60), *westandii* (7). Also, *Asarum canadense* var. *reflexum* (18) and *Bragantia wallichii** (30, 41). Aristolochic acid-I has also been found in the butterfly *Pachlioptera aristolochiae* (20).

¹Isoaristolochic acid, found in *Bragantia wallichii* (30, 41) and in *Aristolochia debilis* (68, 71) is most probably identical with aristolochic acid-I (72).

5. ARISTOLOCHIC ACID-III

C₁₇H₁₁O₇N: 341.2764

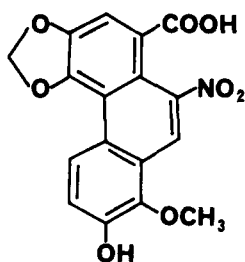
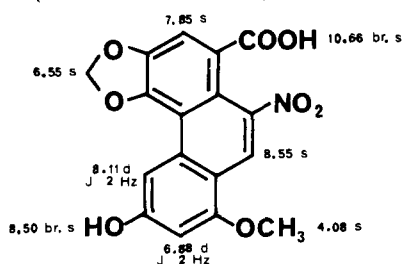
(Me ester): 355.3032

MP: (Me ester) 270-272° (acetone) (47)

MS: (Me ester) Identical with the mass spectrum of the methyl ester of aristolochic acid-I (47).

SOURCES: ARISTOLOCHIACEAE: *Aristolochia argentina* (51), *clematidis* (47), *esperanzae* (51).

6. 7-HYDROXYARISTOLOCHIC ACID-A

C₁₇H₁₃O₈N: 358.2837SOURCE: ARISTOLOCHIACEAE: *Aristolochia debilis* (9). The original literature was not available to the reviewers.7. ARISTOLOCHIC ACID-D
(Aristolochic acid-IVa)C₁₇H₁₁O₈N: 357.2758

(Me ester): 371.3026

MP: 254-259° (DMF-H₂O) (55)254-259° (DMF-*n*-PrOH) (51)

269-271° (MeOH) (34)

(Me ester) 243-250° dec. (55)

UV: (EtOH) 220 (4.47), 242 (4.58), 252 (4.58), 292 (4.14), 325 (4.05) (34)

IR: (Nujol) 3390, 1689, 1520, 1351, 1253, 1176, 1047, 1010, 935, 922 (34)

NMR: (DMSO-*d*₆) (34)SOURCES: ARISTOLOCHIACEAE: *Aristolochia acuminata* (43), *argentina* (51, 55), *clematitis* (55), *esperanzae* (51), *indica* (34, 49), *manshuriensis* (44), *multiflora* (43).

8. ARISTOLOCHIC ACID-B

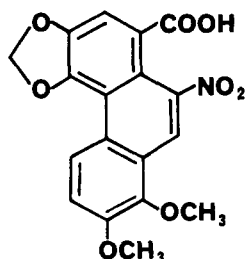
C₁₇H₁₃O₈N: 358.2837

(Me ester): 372.3105

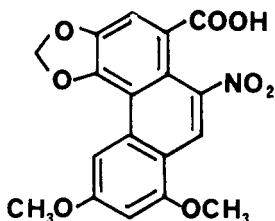
MP: 275-276° dec. (acetone) (66)

UV: (66)

IR: (Nujol) 3484, 1684, 1527, 1351 (66)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia debilis* (67), *fangchi* (66).9. 7-METHOXYARISTOLOCHIC ACID-A²C₁₈H₁₅O₈N: 371.3026SOURCES: ARISTOLOCHIACEAE: *Aristolochia debilis* (9). The original literature was not available to the reviewers.²The corresponding semi-synthetic N-methylactam has been described in Ref. 32.

10. ARISTOLOCHIC ACID-IV



$C_{15}H_{13}O_8N$: 371.3026

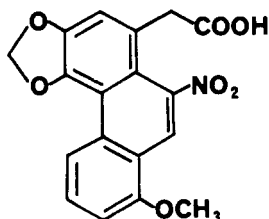
(Me ester): 385.3294

MP: (Me ester) 238–240° ($CH_2Cl_2-C_6H_6$) (47)

MS: (Me ester) 385, 354, 310 (100), 285, 268 (47)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia argentina* (51), *clematitis* (47), *esperanzae* (51), *manshuriensis* (44).

11. DEBILIC ACID



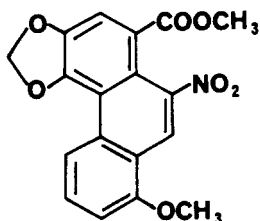
$C_{13}H_{13}O_7N$: 355.3032

MP: >300° (31)

(Me ester) 260° (31)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia debilis* (68, 70), *manshuriensis* (54). The original literature was not available to the reviewers.

12. METHYL ARISTOLOCHATE



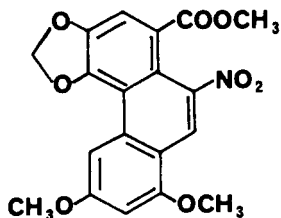
$C_{18}H_{13}O_7N$: 355.0692

MP: 285–286° ($CHCl_3-MeOH$) (49)

IR: (Nujol) 1700, 1510, 1340 (49)

MS: 355, 309 (49)

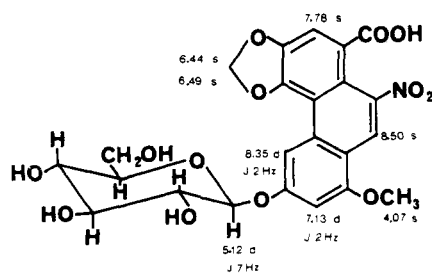
SOURCES: ARISTOLOCHIACEAE: *Aristolochia indica* (49).

13. ARISTOLOCHIC ACID-IV
METHYL ESTER

$C_{19}H_{15}O_8N$: 385.3294

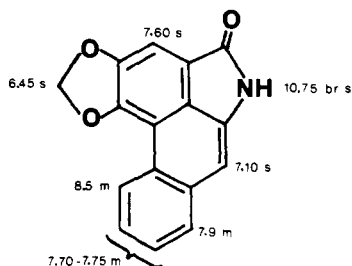
SOURCE: ARISTOLOCHIACEAE: *Aristolochia kwangsiensis* (11). The original literature was not available to the reviewers.

14. ARISTOLOSIDE



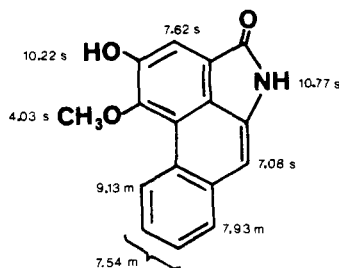
$C_{22}H_{21}O_{13}N$: 519.1012
 MP: 193–196° (MeOH) (44)
 $[\alpha]_D -69.5^\circ$ (c 0.23, MeOH) (44)
 UV: (EtOH) 222 (4.41), 243 (4.51), 252 (4.52),
 318 (4.07), 392 (2.93) (44)
 IR: (KBr) 3380, 1695, 1597, 1517, 1040 (44)
 NMR: (DMSO- d_6) (44)
 MS: 542, 519 (100), 489, 357 (44)
 SOURCES: ARISTOLOCHIACEAE: *Aristolochia manshuriensis* (44).

15. CEPHARANONE-A

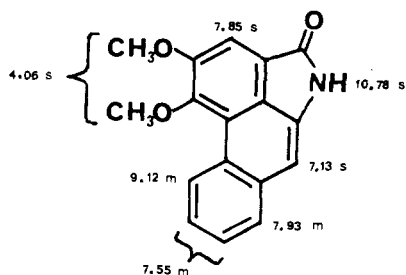


$C_{16}H_9O_3N$: 263.2520
 MP: 308–310° (DMF) (3)
 UV: (EtOH) 225 (4.45), 232 (4.49), 265 (4.46), 277
 (4.53), 288 (4.51), 328 (4.06), 341 (4.04), 376
 (3.93), 393 (3.93) (3)
 IR: (KBr) 3150, 1706, 1690 (3)
 NMR: (DMSO- d_6) (3)
 MS: 263 (100), 235 (6.5), 207 (5.8), 179 (11.2), 177
 (17.4) (3)
 SOURCE: MENISPERMACEAE: *Stephania cepharantha* (3).

16. ARISTOLACTAM-AII

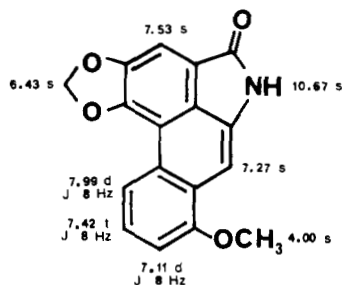


$C_{16}H_{11}O_3N$: 265.2678
 MP: 271 (HOAc) (16)
 UV: (EtOH) 209 (4.39), 235 (4.57), 264 (4.40), 277
 (4.47), 287 (4.47), 317 (3.87), 394 (3.81), 384
 sh (3.81) (16)
 IR: (KBr) 3356, 3268, 1709, 1295 (16)
 NMR: (DMSO- d_6) (16)
 SOURCES: ARISTOLOCHIACEAE: *Aristolochia argentina* (16), *indica* (2).

17. ARISTOLACTAM-BII
(Cepharanone-B)

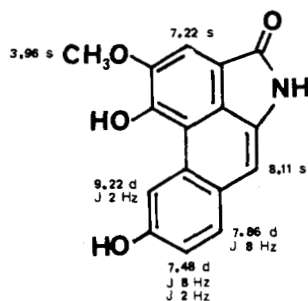
$C_{17}H_{13}O_3N$: 279.2946
 MP: 247–250° (*n*-BuOH) (16)
 264–265° (acetone) (3)
 UV: (EtOH) 232 (4.43), 263 (4.43), 276 (4.48),
 287 (4.48), 319 (4.00), 396 (3.96) (3)
 IR: (KBr) 3226, 1724, 1383 (16)
 NMR: (DMSO- d_6) (16)
 MS: 279, 264, 236, 221, 209 (3)
 SOURCES: ANNONACEAE: *Schefferomitra subaequalis* (19)
 ARISTOLOCHIACEAE: *Aristolochia argentina*
 (16)
 MENISPERMACEAE: *Stephania cepharantha* (3).

18. ARISTOLACTAM
(Aristolactam, aristolactam-I)



$C_{17}H_{11}O_4N$: 293.2782
 MP: 315–317° (sublimes 300°) (34)
 UV: (EtOH) 241 (4.50), 250 (4.47), 259 (4.56), 291 (4.16), 300 (4.15) (66)
 IR: (Nujol) 3175, 1692 (66)
 NMR: (DMSO- d_6) (34)
 SOURCES: ARISTOLOCHIACEAE: *Aristolochia argentina* (51), *debilis* (67), *fangchi* (66), *indica* (34), *rotunda* (5).

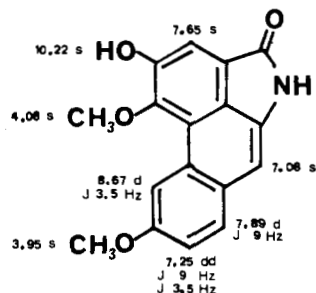
19. DORYFLAVINE



$C_{18}H_{11}O_4N$: 281.2672
 MP: 339° (MeOH) (8)
 UV: (MeOH) 207 (4.42), 230 (4.59), 251 (4.45), 260 (4.41), 277 (4.32), 290 (4.34), 320 (4.11), 400 (3.91) (19)
 IR: (KBr) 3350, 3200, 1700, 1500, 1425, 1361, 1300, 1000, 750 (8)
 NMR: (Pyridine- d_5) (8)
 MS: 281 (100), 266 (62), 238 (18), 210 (6), 182 (18), 140 (12), 119 (12), 90 (10), 78 (6), 63 (6) (8)
 SOURCE: MONIMIACEAE: *Doryphora sassafras* (8).

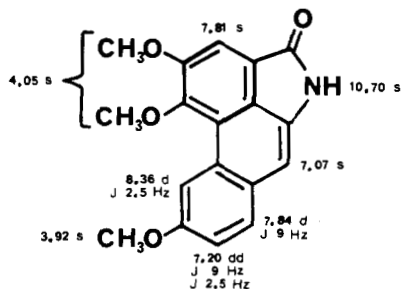
The structural assignment is tentative.

20. ARISTOLACTAM-AIII



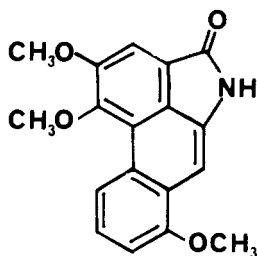
$C_{17}H_{13}O_4N$: 295.2940
 MP: 275° (HOAc) (16)
 UV: (EtOH) 216 (4.34), 238 (4.58), 253 (4.42), 280 (4.36), 292 (4.36), 322 (3.96), 401 (3.84) (16)
 IR: (KBr) 3378, 3226, 1684, 1164 (16)
 NMR: (DMSO- d_6) (16)
 SOURCE: ARISTOLOCHIACEAE: *Aristolochia argentina* (16)

21. ARISTOLACTAM-BIII



$C_{18}H_{15}O_4N$: 309.3208
 MP: 225° (*n*-PrOH-*n*-BuOH) (16)
 UV: (EtOH) 236 (4.53), 255 (4.38), 262 (4.40), 281 (4.30), 293 (4.33), 313 (4.01), 321 (4.01), 399 (3.80) (16)
 IR: (KBr) 3236, 1730, 1381, 1244 (16)
 NMR: (DMSO- d_6) (16)
 SOURCE: ARISTOLOCHIACEAE: *Aristolochia argentina* (16).

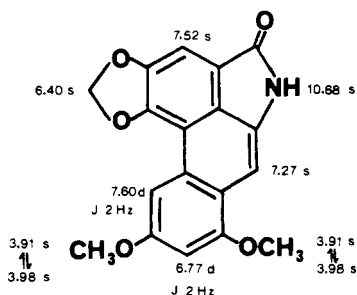
22. TALISCANINE

C₁₈H₁₅O₄N: 309.3208

MP: 272-273° (40)

SOURCE: ARISTOLOCHIACEAE: *Aristolochia taliscana* (40).

23. ARISTOLOCHIC ACID-D METHYL ETHER LACTAM

C₁₈H₁₃O₅N: 323.3044

MP: 350-355° (sublimes >300°) (34)

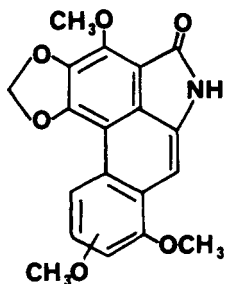
UV: (EtOH) 240 (4.45), 262 (4.37), 290 (4.07), 330 (4.05), 334 (3.85) (34)

IR: (Nujol) 3164, 1683, 1428, 1333, 1168, 1129, 1052, 1010, 948, 935 (34)

NMR: (DMSO-*d*₆) (34)SOURCES: ARISTOLOCHIACEAE: *Aristolochia indica* (34)

Structural assignment is uncertain.

24. ARISTORED

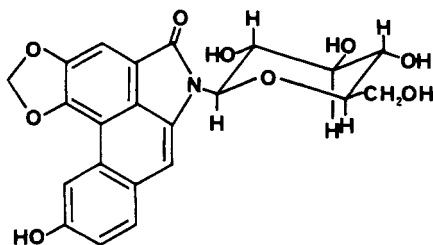
C₁₉H₁₇O₆N: 355.3464

MP: 286.5 (EtOH) (14)

UV: (EtOH) 253 (4.63), 265 (4.50), 294 (4.29), 300 (4.28), 305 (4.27), 335 sh (3.77), 352 sh (3.70), 395 (3.91) (14)

SOURCES: ARISTOLOCHIACEAE: *Aristolochia bracteata* (27), *reticulata* (14, 15), *serpentaria* (15).

25. ARISTOLACTAM-C N-β-D-GLUCOSIDE

C₂₂H₁₉O₉N: 441.3934

MP: >320° (1)

[α]_D (Methyl ether tetraacetate)-97.1° (c 0.7, CHCl₃) (1)

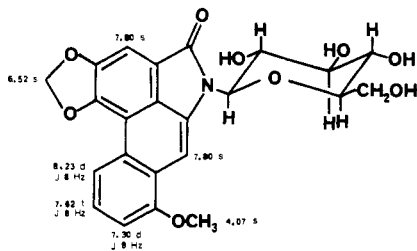
IR: (Methyl ether tetraacetate) (KBr) 1750, 1710, 1620, 1510, 1420, 1370, 1230, 1030 (1)

NMR: (Methyl ether tetraacetate) (1)

MS: 308, 292, 279 (1)

SOURCE: ARISTOLOCHIACEAE: *Aristolochia indica* (1).

26. ARISTOLACTAM N- β -D-
GLUCOSIDE
(Aristolactam β -D-glucoside)



$C_{22}H_{31}O_9N$: 455.4202

MP: 331–333° (MeOH–H₂O) (34)

$[\alpha]^{25}_D -14^\circ$ (c 0.02, H₂O) (34)

$[\alpha]^{25}_D -18^\circ$ (c 0.11, DMF) (34)

UV: (EtOH) 238 (4.49), 243 (4.52), 249 (4.50),
258 (4.56), 290 (4.18), 298 (4.18), 328 (3.98)
(34)

IR: (Nujol) 3546, 3390, 1689 (34)

NMR: (DMSO-*d*₆) (34)

SOURCE: ARISTOLOCHIACEAE: *Aristolochia indica* (1, 34, 49).

Names of Aristolochic Acids and Aristolactams

Aristolactam	18	Aristolochic acid-B	8
Aristolactam-I	18	Aristolochic acid-C	3
Aristolactam-AII	16	Aristolochic acid-D	7
Aristolactam-AIII	20	Aristolochic acid-IV methyl ester	13
Aristolactam-BII	17	Aristolochic acid-D methyl ether lactam	23
Aristolactam-BIII	21	Aristolactam	18
Aristolactam-C N- β -D-glucoside	25	Aristoloid	14
Aristolactam N- β -D-glucoside	26	Aristored	24
Aristolochic acid-I	4	Cepharanone A	15
Aristolochic acid-Ia	2	Cepharanone B	17
Aristolochic acid-II	1	Debilic acid	11
Aristolochic acid-III	5	Doryflavine	19
Aristolochic acid-IIIa	3	7-Hydroxyaristolochic acid-A	6
Aristolochic acid-IV	10	7-Methoxyaristolochic acid-A	9
Aristolochic acid-IVa	7	Methyl aristolochate	12
Aristolochic acid-A	4	Taliscanine	22
Aristolochic acid	4		

Botanical Occurrence

ANNONACEAE

Schefferomitra subaequalis

Aristolactam-BII
 17 |

ARISTOLOCHIACEAE

Aristolochia acuminata

Aristolochic acid-I
 4 |

Aristolochic acid-D
 7 |

Aristolochia argentina

Aristolochic acid-I
 4 |

Aristolochic acid-II
 1 |

Aristolochic acid-III
 5 |

Aristolochic acid-IV
 10 |

Aristolochic acid-D
 7 |

Aristolactam
 18 |

Aristolactam-AII
 16 |

Aristolactam-AIII
 20 |

Aristolactam-BII
 17 |

Aristolactam-BIII
 21 |

Aristolochia badamae

Aristolochic acid-I
 4 |

Aristolochia baetica

Aristolochic acid-I
 4 |

Aristolochia bracteata

Aristolochic acid-I
 4 |

Aristored
 24 |

Aristolochia chilensis

Aristolochic acid-I
 4 |

Aristolochic acid-Ia
 2 |

Aristolochia clematitidis

Aristolochic acid-I
 4 |

Aristolochic acid-II
 1 |

Aristolochic acid-III
 5 |

Aristolochic acid-IV
 10 |

Aristolochic acid-D
 7 |

Aristolochia debilis

Aristolochic acid-I
 4 |

Aristolochic acid-II
 1 |

Aristolochic acid-B
 8 |

Aristolochic acid-C
 3 |

Aristolochic acid-D
 7 |

Aristolactam
 18 |

Debilic acid
 11 |

7-Hydroxyaristolochic acid-A
 6 |

7-Methoxyaristolochic acid-A
 9 |

Aristolochia elegans

Aristolochic acid-I
 4 |

Aristolochia esperanzae

Aristolochic acid-I
 4 |

Aristolochic acid-II
 1 |

Aristolochic acid-III
 5 |

Aristolochic acid-IV
 10 |

Aristolochic acid-D
 7 |

Aristolochia fangchi

Aristolochic acid-I
 4 |

Aristolochic acid-B
 8 |

Aristolochic acid-C
 3 |

Aristolactam
 18 |

Aristolochia fimbriata

Aristolochic acid-I
 4 |

Aristolochia graffilii

Aristolochic acid-I
 4 |

Aristolochia indica

Aristolochic acid-I
 4 |

Aristolochic acid-D
 7 |

Aristolochic acid-D methyl ether

lactam
 23 |

Methyl aristolochate
 12 |

Aristolactam
 18 |

Botanical Occurrence. Continued

Aristolactam-AII.....	16	<i>Aristolochia reticulata</i>	
Aristolactam N- β -D-glucoside.....	26	Aristolochic acid-I.....	4
Aristolactam-C N- β -D-glucoside.....	25	Aristored.....	24
<i>Aristolochia kaempferi</i>		<i>Aristolochia rotunda</i>	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
<i>Aristolochia kwangsiensis</i>		Aristolochic acid-II.....	1
Aristolochic acid-I.....	4	Aristolochic acid-C.....	3
Aristolochic acid-IV methyl ester.....	13	Aristolactam.....	18
<i>Aristolochia longa</i>		<i>Aristolochia serpentaria</i>	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
Aristolochic acid-II.....	1	Aristored.....	24
<i>Aristolochia manshuriensis</i>		<i>Aristolochia siphon</i> (syn. <i>A. durior</i>)	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
Aristolochic acid-II.....	1	Aristolochic acid-II.....	1
Aristolochic acid-IV.....	10	<i>Aristolochia taliscana</i>	
Aristolochic acid-D.....	7	Taliscanine.....	22
Aristolosite.....	14	<i>Aristolochia watsonii</i>	
Debilic acid.....	11	Aristolochic acid-C.....	3
<i>Aristolochia maurorum</i>		<i>Aristolochia westandii</i>	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
<i>Aristolochia maxima</i>		<i>Asarum canadense</i>	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
<i>Aristolochia mollissima</i>		<i>Bragantia wallichii</i>	
Aristolochic acid-I.....	4	Aristolochic acid-I.....	4
<i>Aristolochia multiflora</i>		MENISPERMACEAE	
Aristolochic acid-I.....	4	<i>Stephania cepharantha</i>	
Aristolochic acid-D.....	7	Aristolactam-BII.....	17
<i>Aristolochia ornithocephala</i>		Cepharanone-A.....	15
Aristolochic acid-I.....	4	MONIMIACEAE	
<i>Aristolochia pendurata</i>		<i>Doryphora sassafras</i>	
Aristolochic acid-I.....	4	Doryflavine.....	19

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