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THE ISOINDOLOBENZAZEPINE ALKALOIDS

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Abstract: Three Chilean barberries, Berberis actinacantha Mart. ex Schult., B. darwinii Hook and B. valdiviana Phil. (Berberidaceae), have yielded several new isoindolobenzazepine and protoberberine alkaloids. Novel isoindolobenzazepines are (±)-13-deoxychilenine (9), pictonamine (10), chileninone (12), (±)-chilenamine (18) and (±)-palmanine (19). Highly oxidized protoberberines of particular interest include (±)-O-methylprechilenine (6) and (±)-prepseudopalmanine (21), together with 13-methoxy-8-oxyberberine (3). Isoindolobenzazepine alkaloids arise biogenetically from the rearrangement of highly oxidized protoberberines.

Two recently characterized alkaloids belonging to the new class of isoindolobenzazepines are (±)-chilenine (7) and (±)-lennoxamine (11). The first of these compounds was originally found in Chilean Berberis empetrifolia Lam. (Berberidaceae),[1] while lennoxamine was isolated from B. darwinii Hook, also of Chilean origin.[2]

The biogenesis of chilenine (7) was postulated to proceed by oxidation of the quaternary salt berberine (1), found in all Berberis species, to the putative prechilenine (4) which could then undergo skeletal rearrangement to 7.[1] Dehydration and reduction of chilenine (7) would lead to lennoxamine (11).[2] This sequence was buttressed by the fact that it is known that berberine (1) may be oxidized in vitro to prechilenine (4) which can be rearranged to chilenine (7) in the presence of ammonium hydroxide.[3]

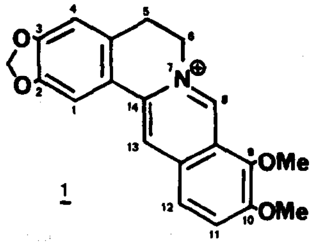
Presently, we wish to report on further work on three Chilean Berberis species, namely B. actinacantha Mart. ex Schult., B. darwinii Hook and B. valdiviana Phil., which has led to the isolation of the hitherto hypothetical alkaloid (±)-prechilenine (4), in the form of its O-methyl ether 6. Another highly oxidized new protoberberine we have found is (±)-prepseudopalmanine (21). Very significantly, these alkaloids are accompanied by an array of novel isoindolobenzazepines including (±)-deoxychilenine (9), pictonamine (10), chileninone (12), (±)-chilenamine (18), and (±)-palmanine (19). The picture that emerges from this isolation study clarifies both the genesis and the catabolism of the isoindolobenzazepines within members of the botanical family Berberidaceae.

The original enzymatic oxidation of berberine (1) in the plant probably leads to the reactive 13-hydroxy-8-oxyberberine (2), which has not yet been isolated as a natural product.[4] We have now found that this phenol may undergo in vivo O-methylation to the yellow 13-methoxy-8-oxyberberine (3),[4] $C_{21}H_{19}NO_6$, ν max $CHCl_3$ 1650 cm^{-1}, which is present in B. darwinii. The high resolution $CDCl_3$ NMR spectrum of this new alkaloid has been summarized around expression 3. A notable feature of this spectrum is the appreciable downfield shift (δ 7.98) of the singlet signal for H-1 due to the proximity of this proton to the methoxyl group oxygen at C-13.

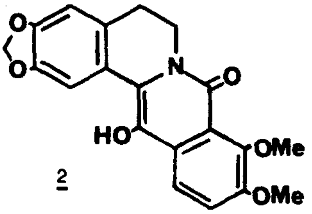
An *in vivo* alternative to the O-methylation of 13-hydroxy-8-oxyberberine (2) consists in its further oxidation to prechilenine (4), here obtained for the first time as a natural product in the form of its O-methyl ether 6, $C_{21}H_{19}NO_7$, ν max $CHCl_3$ 1665 and 1725 cm^{-1}. The NMR spectrum quoted around expression 6 is very close to the one originally reported at 60 MHz for material derived synthetically from oxidation of berberine (1).[3] The biogenesis of O-methylprechilenine (6) in all likelihood proceeds from prechilenine (4). This transformation has been duplicated in the laboratory since it has been shown that upon standing in methanol, particularly under acid conditions, 4 can undergo overall O-methylation to 6 through the intermediacy of azaquinonium cation 5 which can readily add methanol.[3]

As an alternative to O-methylation, prechilenine (4) may, in the plant, undergo isomerization to the isoindolobenzazepine chilenine (7), which as indicated earlier had been found in *B. empetrifolia* Lam.,[1] and which we have now reisolated from two of our barberries, *B. actinacantha* and *B. darwinii*.

Four biogenetic derivatives of (±)-chilenine (7) we now describe are the colorless (±)-13-deoxychilenine (9), the yellow pictonamine (10), the deep red chileninone (12) and the colorless (±)-chilenamine (18).



1



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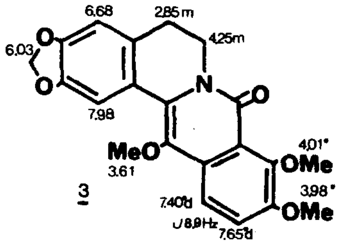

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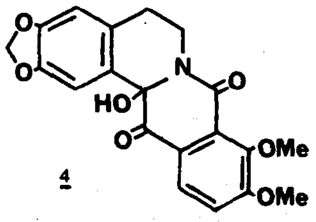

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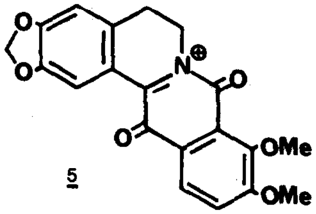

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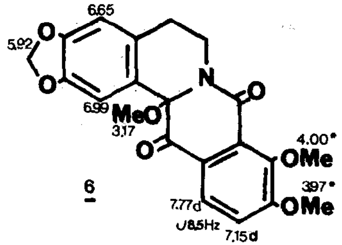
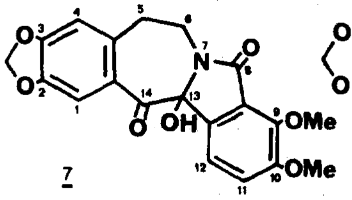


6

H-5 2.78,2.87 m
H-6 3.18,5.03 m



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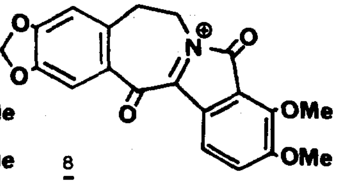

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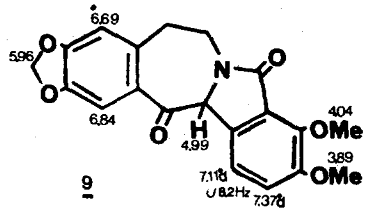
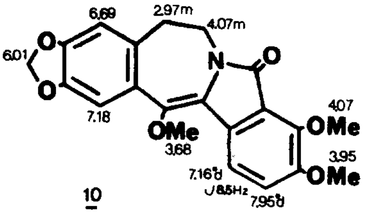


9

H-5 2.70,3.37m
H-6 3.24,4.50m



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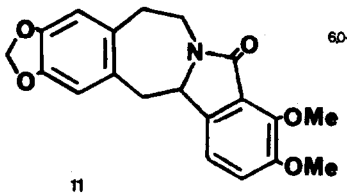

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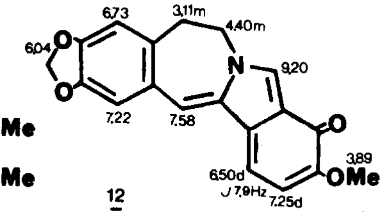
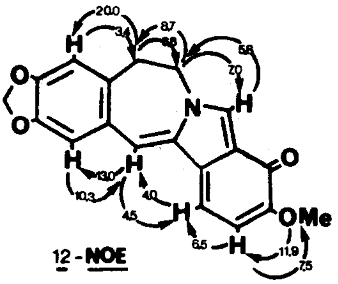
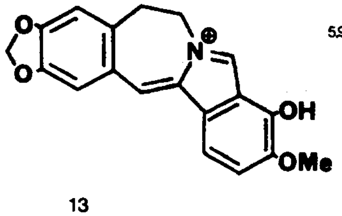


12



12 - **NOE**



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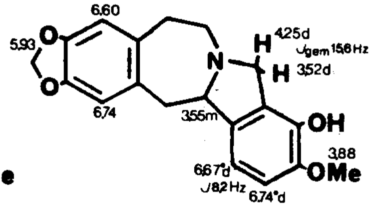
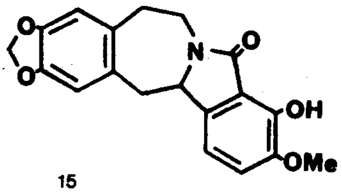


14

H-5 2.82,3.13 m
H-6 2.85,3.19 m
H-14 2.83,3.23 m



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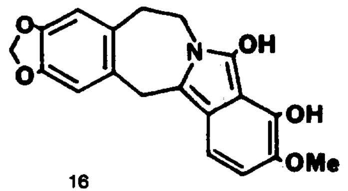

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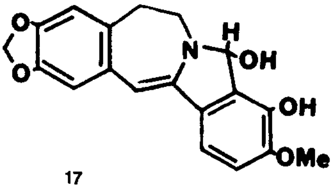
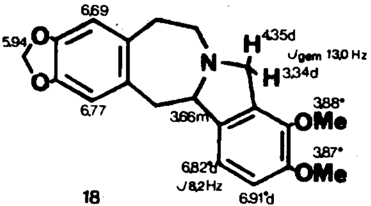
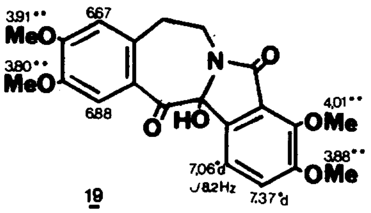


17



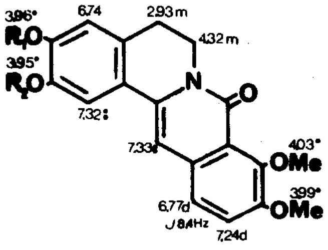
18

H-5 2.87,3.10 m
H-6 2.85,3.10 m
H-14 2.87,2.81 m



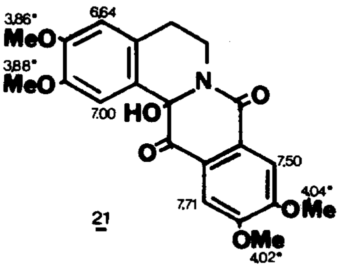
19

H-5 3.32 m
H-6 3.81, 4.26 m



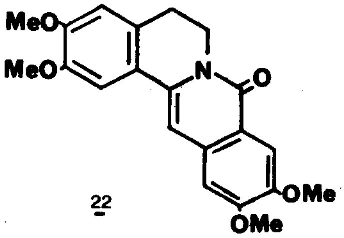
20a $R_1+R_2 = CH_2$

20b $R_1 = R_2 = CH_3$ (NMR)



21

H-5 2.68,3.87 m
H-6 3.16,4.90 m



22

(±)-13-Deoxychilenine (9), $C_{20}H_{17}NO_6$, ν max $CHCl_3$ 1705 cm^{-1}, was found in B. actinacantha. A conspicuous feature of its NMR spectrum was the one-proton singlet at δ 4.99 representing H-13. This ketolactam is most likely formed from chilenine through dehydration to cation 8 which can suffer ready reduction of the iminium bond.

(±)-Pictonamine (10), $C_{21}H_{19}NO_6$, ν max $CHCl_3$ 1685 cm^{-1}, located in B. darwinii, is simply the methyl enol ether of 13-deoxychilenine (9). Species 10 had in fact been prepared synthetically from chilenine (7) in a series of in vitro experiments, and the natural and synthetic samples proved to be identical.[5] In order to insure that pictonamine was a true alkaloid and not an artifact of isolation, 13-deoxychilenine (9) was dissolved in methanol and the solution allowed to stand 24 h. A little silica gel was then added, and the mixture was kept for another 24 h. No pictonamine (10) could be detected from these conditions.

Maybe the most interesting of the new isoindolobenzazepines we describe is the red chileninone (12) which must be common to many Berberis species since it was isolated from all three plants under consideration. The alkaloid analyzed for $C_{19}H_{15}NO_4$, ν max $CHCl_3$ 1625, 1645 cm^{-1}, and its NMR spectrum is presented around expression 12. In the aromatic region of the spectrum, four one-proton singlets and two coupled one-proton doublets were in evidence. To ascertain the assignments of the aromatic protons, we had recourse to NOEDS studies.[6] Irradiation of the H-1 singlet (δ 7.22) caused a 10.3% NOE of H-14 (δ 7.58), while irradiation of the H-4 singlet (δ 6.73) led to a 3.4% enhancement of the H-5 multiplet (δ 3.11). Furthermore, irradiation of the methoxyl singlet (δ 3.89) resulted in an 11.9% NOE of the H-11 doublet at δ 7.25. These data and others have been summarized in expression 12-NOE.

In accord with its enamine structure, chileninone (12) turned yellow upon addition of acid, due to generation of iminium cation 13. Sodium borohydride reduction of the alkaloid provided the colorless phenolic derivative 14, $C_{19}H_{19}NO_4$.

The biogenesis of chileninone (12) may be understood in terms of nucleophilic O-demethylation of lennoxamine (11) to phenol 15. Isomerization of the double bonds would lead to isoindole 16 and pseudobase 17, and eventual loss of water would provide the desired product 12-13.

A related isoindolobenzazepine present in B. darwinii is (±)-chilenamine (18), $C_{20}H_{21}NO_4$. This alkaloid had previously been known synthetically as "Schöpf's Base VI", and the present report is the first of its isolation from a natural source.[7] The genesis of chilenamine (18) is not clear at this stage. It could arise from in vivo reduction of chileninone (12) to amine 14, followed by enzymatic O-methylation. Alternatively, it could be produced from the stepwise reduction of chilenine (7) in a sequence that does not involve O-demethylation, although it must be stated that nature does not as a rule readily reduce amidic systems.

Not surprisingly, the known alkaloid 8-oxyberberine (20a) was present both in B. actinacantha and B. darwinii.[8]

While all of the alkaloids we have described so far originate from berberine (1), analogs of this common protoberberinium salt differing in the nature or location of the aromatic substituents may also undergo parallel oxidations and isomerizations. Thus, from B. actinacantha, we have obtained the isoindolobenzazepine palmanine (19), $C_{21}H_{21}NO_7$, ν max $CHCl_3$ 1710, 3350 cm^{-1}, which is the tetramethoxy analog of chilenine (7). This material is accompanied in the plant by the yellow fluorescent 8-oxypalmatine (20b). Furthermore, from B. darwinii, we collected a small quantity of the highly oxidized protoberberine prepseudopalmanine (21), $C_{21}H_{21}NO_7$, ν max KBr 1632, 1672 cm^{-1}, which had previously been prepared in vitro through pyridine chlorochromate oxidation of 8-oxypseudopalmatine (22).[9]

With the present identification of five new isoindolobenzazepines, this class of natural products, all of whose members are optically inactive, may be considered one of the important modifications within the realm of isoquinoline and isoquinoline derived alkaloids. Isoindolobenzazepines thus take their place, alongside the protopines, phthalideisoquinolines, benzophenanthridines, spirobenzylisoquinolines and secoberbines, all of which are also derived from protoberberines.

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TABLE: Physical and Spectral Characteristics of the Alkaloids

13-Methoxy-8-oxyberberine (3): m.p. 197-200° C ($CHCl_3$-hexane) (lit.[4] 194-195° C from MeOH); λ max MeOH 233, 255 sh, 332, 341, 344, 346, 374 sh, 394 sh nm (log ε 3.66, 3.31, 3.49, 3.48, 3.48, 3.47, 3.20, 3.00); m/z 382 $(M + 1)^+$ (9), 381 $(M)^+$ (37), 367 (23), 366 (100), 336 (6), 322 (5), 308 (3); high res. ms M^+ calc. 381.1212, fd. 381.1235.

O-Methylprechilenine (6): Amorphous and unstable; λ max MeOH 235, 261 sh, 289, 325 nm (log ε 4.37, 4.01, 3.92, 3.86); m/z 398 $(M + 1)^+$ (24), 397 $(M)^+$ (99), 383 (22), 382 (89), 368 (19), 367 (58), 366 (100), 365 (17), 364 (49), 354 (11), 352 (16), 339 (12), 338 (58), 322 (10), 204 (37).

13-Deoxychilenine (9): Amorphous; λ max MeOH 213 sh, 291, 308 nm (log ε 4.20, 3.44, 3.02); m/z 368 $(M + 1)^+$ (15), 367 $(M)^+$ (64), 352 (10), 351 (22), 340 (5), 339 (26), 338 (100), 336 (9), 322 (10), 308 (18), 294 (12), 280 (5), 265 (4), 220 (17), 208 (12), 192 (6), 190 (6), 176 (40), 175 (22), 165 (12), 160 (21), 135 (11), 107 (12); high res. ms M^+ 367.1056, fd. 367.1069.

Pictonamine (10): m.p. 228-230° C (MeOH) (lit.[5] 231-232° C from MeOH); λ max MeOH 235, 274, 305,325,379, 399 sh nm (log ε 3.35, 2.92, 3.02, 2.95, 3.51, 3.43); m/z 382 $(M + 1)^+$ (16), 381 $(M)^+$ (73), 367 (22), 366 (100), 338 (40), 322 (9), 294 (12), 190 (6), 176 (5), 175 (8), 147 (11); high res. ms M^+ calc. 381.1212, fd. 381.1201.

Chileninone (12): Amorphous; λ max MeOH 238, 277, 328, 389 nm (log ε 4.06,4.03, 3.59, 3.60); λ max MeOH+H^+ 232, 272, 355, 438 nm (log ε 4.02, 4.03, 3.84, 3.28); m/z 322 $(M + 1)^+$ (32), 321 $(M)^+$ (84), 320 (45), 308 (24), 307 (20), 306 (37), 304 (20), 293 (12), 292 (41), 291 (12), 279 (23), 278 (100), 263 (20), 248 (11), 220 (17), 219 (14), 207 (10), 206 (12), 205 (12), 204 (14), 192 (11), 191 (23), 190 (14); high res. ms M^+ calc. 321.1001, fd. 321.1027.

9-O-Demethylchilenamine (14): Amorphous; λ max MeOH 229 sh, 286, 298 sh nm (log ε 4.10, 3.74, 3.59); m/z 326 $(M + 1)^+$ (15), 325 (70), 324 (37), 308 (10), 177 (12), 176 (100), 174 (31), 151 (12), 150 (47), 149 (17), 135 (20).

Chilenamine (18): Amorphous; λ max MeOH 228 sh, 284, 286 sh nm (log ε 4.05, 3.75, 3.73); m/z 340 $(M + 1)^+$ (23), 339 (100), 338 (6), 337 (7), 324 (19), 322 (2), 260 (5), 244 (4), 232 (3), 204 (3), 203 (4), 197 (6), 191 (6), 190 (3), 176 (8), 175 (3), 174 (3), 170 (3), 169 (25), 163 (39), 162 (29); high res. ms M^+ calc. 339.1470, fd. 339.1459.

Palmanine (19): Amorphous; λ max MeOH 216,235, 279, 314 nm (log ε 4.44, 4.32, 3.84, 3.83); m/z 400 $(M + 1)^+$ (9), 399 $(M)^+$ (38), 383 (8), 370 (3), 354 (14), 340 (6), 220 (51), 206 (31), 193 (15), 192 (100), 179 (7), 178 (5), 177 (9), 165 (48), 164 (87), 151 (37).

8-Oxypalmatine (20): Amorphous; λ max MeOH 226, 255 sh, 280, 337, 367, 389 nm (log ε 4.65, 4.23, 4.02, 4.46, 4.19, 4.00); m/z 368 $(M + 1)^+$ (23), 367 $(M)^+$ (100), 353 (11), 352 (49), 350 (4), 338 (21), 336 (11), 324 (10), 322 (5), 308 (11), 294 (4), 280 (4), 181 (4).

Prepseudopalmanine (21): Amorphous; λ max MeOH 252, 289 sh, 330 sh nm (log ε 4.61, 3.99, 3.74); m/z 400 $(M +1)^+$ (1.5), 399 $(M)^+$ (6), 384 (24), 383 (100), 382 (36), 381 (71), 380 (25), 368 (29), 366 (26), 365 (7), 354 (13), 353 (12), 352 (42), 340 (10), 330 (15), 337 (6), 336 (8), 324 (15), 322 (14), 310 (7), 294 (7).

EXPERIMENTAL

General Experimental Procedures: The dried, powdered plants were first defatted with petroleum ether. Extraction was with cold ethanol, and the evaporation of the solvent was carried out with the minimum application of heat. The extracts were fractionated using 3N HCl and then dil. ammonium hydroxide. The alkaloidal fractions were subjected to extensive column chromatography on silica gel, and to thin layer chromatography on preprepared Merck Silica Gel G glass plates. NMR spectra were obtained at 200 MHz in $CDCl_3$, but the NOEDS data were gathered on a 360 MHz spectrometer.

B. actinacantha (7.3 kg, dry stems and twigs) was collected on Cerro Lo Curro, near Ciudad Santiago, and yielded: Chilenine (**7**), 10 mg; 13-deoxychilenine (**9**), 2 mg; chileninone (**12**), 16 mg (this alkaloid was found only in the twigs extracts); palmanine (**19**), 4 mg; 8-oxyberberine (**20a**), 250 mg; 8-oxypalmatine (**20b**), 41 mg.

B. darwinii (18 kg, dry stems) was obtained in the vicinity of Ciudad Osorno in south central Chile, and gave: 13-methoxy-8-oxyberberine (**3**), 12 mg; O-methylprechilenine (**6**), 4 mg; chilenine (**7**), 22 mg; pictonamine (10), 28 mg; lennoxamine (**11**), 3 mg; chileninone (**12**), 5 mg; chilenamine (18), 1 mg; 8-oxyberberine (**20a**), 10 mg; prepseudopalmanine (**21**), 1 mg; 8-oxypalmatine (**20b**), 6 mg.

B. valdiviana (20 kg, dry stems) was collected near Ciudad Santiago, and furnished chileninone (**12**), 4 mg.

Reduction of Chileninone: The red alkaloid **12** was reduced with excess sodium borohydride in methanol. Purification was by tlc using the system benzene-methanol-ammonium hydroxide (95:5:trace), to afford 9-O-demethylchilenamine (**14**); R_f 0.60.

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