NEW ALKALOIDS FROM *FUMARIA PARVIFLORA*[1]

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ABSTRACT.—Fumariflorine ethyl ester (**22**) has been isolated from the work-up of the alkaloids of *Fumaria parviflora*. Since ethyl esters are unknown among alkaloids and since ethyl alcohol was used during the isolation process, the true alkaloid is most probably fumariflorine (**23**). Fumariflorine may be considered the first representative of a new but small group of isoquinoline alkaloids, namely the O-(β-dimethylaminoethyl)benzoic acids, which originate from the breakdown of phthalideisoquinolines. Another new alkaloid of *F. parviflora* is the glycosidic spirobenzylisoquinoline parviflorine (**30**) which corresponds to (+)-parfumine-β-D-glucoside and whose acid hydrolysis yields (+)-parfumine (**14**) and D-glucose. Dihydroparfumine (**17**) corresponds in all respects to the alkaloid fumaritine and shows a cd curve with a positive Davydov split, pointing to the absolute configuration indicated. This same absolute configuration is prevalent among naturally occurring spirobenzylisoquinolines. A third new alkaloid found is the phthalideisoquinoline base fumaramidine (**21**).

The creeper *Fumaria parviflora* Lam. (Fumariaceae) is botanically identical with *Fumaria indica* Pugsley (1). Several studies of this plant show it to be a generous source of isoquinoline alkaloids, most, if not all, of which are biogenetically derived from (+)-reticuline (**1**). The alkaloids include the protoberberines (−)-stylopine (**2**), coptisine (**3**), and dehydrocheilanthifoline (**4**); the phthalideisoquinolines (+)-bicuculline (**5**), *N*-methylhydrasteine (**6**), narceineimide (**7**), fumaridine (**8**), and fumaramine (**9**); the protoberberines protopine (**10**), and cryptopine (**11**); the benzophenanthridine sanguinarine (**12**); and the spirobenzylisoquinolines fumariline (**13**), parfumine (**14**), and parfumidine (**15**) (2).

F. parviflora is widespread in Pakistan, where it is commonly known as Pit Papra and where its extracts are used in folk medicine as a blood purifier and as an anthelmintic, as well as in the treatment of skin diseases and diarrhea (3). In our hands, thin layer chromatography of the crude alkaloidal extracts indicated the presence of almost twice as many alkaloids as had been previously reported, so that a detailed reinvestigation of this plant was warranted.

The dried alcoholic extract from 8 kg of the dried whole plant was extracted with 5% hydrochloric acid. The aqueous acidic layer was then extracted with chloroform. Evaporation of the organic solvent furnished Extract A.

The acidic aqueous part was made alkaline with ammonium hydroxide and again extracted with chloroform. Removal of the solvent provided Extract B.

Extract A was placed on a silica gel column which was eluted with chloroform and then with chloroform containing increasing amounts of methanol. This procedure yielded a series of known isoquinoline alkaloids, namely, (−)-stylopine (**2**), (+)-fumariline (**13**), (+)-parfumidine (**15**), (+)-parfumine (**14**), (+)-bicuculline (**5**), (+)-α-hydrastine (**16**), *N*-methylhydrasteine (**6**), fumaritine (**17**), (+)-isoboldine (**18**), protopine (**10**), and coptisine (**3**). Of these alkaloids, the spirobenzylisoquinoline fumaritine (**17**) had not previously been reported in

[1]Parts of this paper have appeared in communication form, see S. F. Hussain and M. Shamma, *Tetrahedron Lett.*, 1909 (1980); and S. F. Hussain and M. Shamma, *Tetrahedron Lett.*, 1693 (1980).

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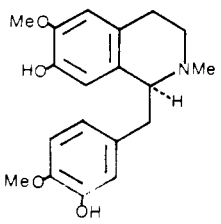

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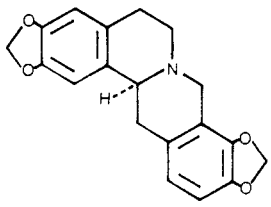

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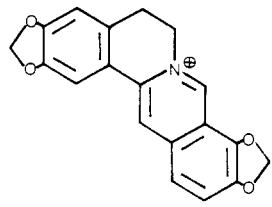

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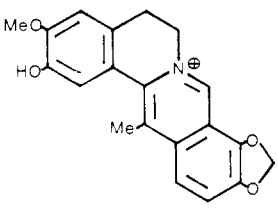

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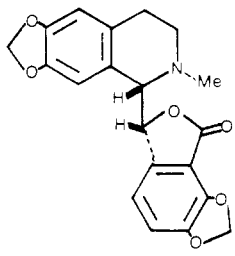

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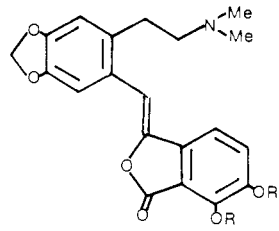
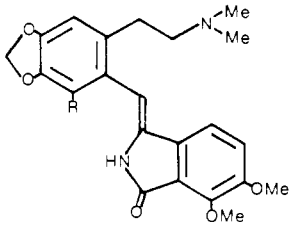
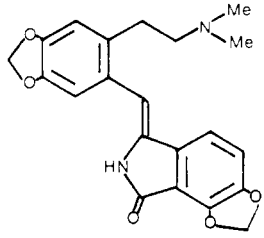


6, R = Me
6a, R + R = CH_2



7, R = OMe
8, R = H



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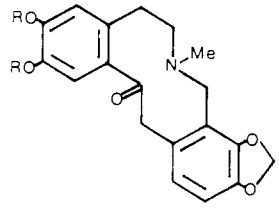

10, R + R = CH_2
11, R = Me

F. parviflora, while the aporphine (+)-isoboldine (**18**) had never been found in a member of the Fumariaceae.[3]

Extract B was then chromatographed by essentially the same procedure as for Extract A. The compounds thus isolated proved to be (+)-parfumine (**14**), noroxyhydrastinine (**19**), protopine (**10**), (+)-isoboldine (**18**), fumaramine (**9**), and fumaridine (**8**). In addition to these, three new alkaloids were obtained from Extract B.

The first of the new alkaloids, labeled fumaramidine, was separated by tlc from the accompanying fumaramine (**9**) only with difficulty and exhibited a

[3]For a listing of the isoquinoline alkaloids, see T. Kametani, *The Chemistry of the Isoquinoline Alkaloids*, Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan (1974).

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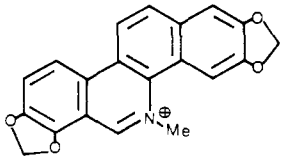

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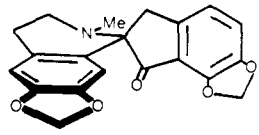

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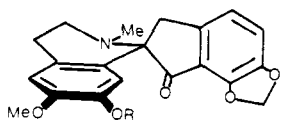
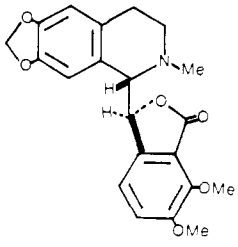


14, R = H
15, R = Me



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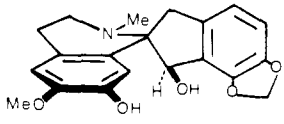

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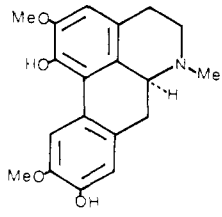

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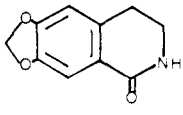

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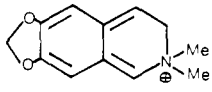

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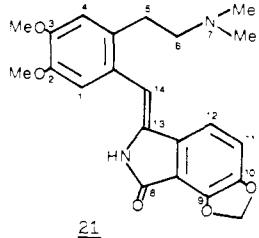

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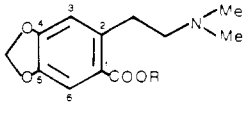
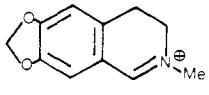


22, R = Et
23, R = H



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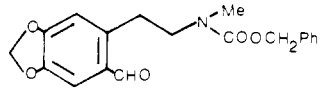

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molecular ion, *m/e* 396, which indicated the molecular formula $C_{22}H_{24}N_2O_5$. It is, therefore, structurally isomeric with the known imide fumaridine (**8**) (4). Its base peak, *m/e* 58, is diagnostic of a β-dimethylaminoethyl side chain (4). The presence of an *m/e* 220 peak pointed to formation of cation **20**, so fumaramidine must correspond to expression **21** and is a hitherto unreported phthalideisoquinoline analog. This conclusion is further supported by the nmr spectrum, whose salient features are two *N*-methyl groups, two methoxyls, a methylenedioxy, three vinylic singlet protons, and a doublet of doublets for the aromatic C-11 and C-12 protons. Very significantly, the methylenedioxy singlet in fumaramidine (**21**) is found downfield at δ6.20 due to the neighboring imide carbonyl. In fumaridine (**8**), on the other hand, it is the C-9 methoxyl group which is located relatively downfield at δ4.12 because of a similar situation, while the ring A

methylenedioxy protons are upfield at δ5.98 (table 2). It is worth noting also that while *N*-methylhydrasteine (**6**) gives a bright greenish-blue fluorescence under long wave length uv light, fumaramine (**9**), fumaridine (**8**), and fumaramidine (**21**) show a dark blue fluorescence under identical conditions.

Fumariflorine ethyl ester (**22**), the second new compound isolated, showed a base peak *m/e* 58 in its mass spectrum, again denoting the presence of a β-dimethylaminoethyl side chain. The molecular ion *m/e* 265 indicated the formula $C_{14}H_{19}NO_4$, while another important peak, *m/e* 220, pointed to the facile loss of an ethoxyl group from the molecular ion. The ir spectrum showed ν max ($CHCl_3$) 1710 cm^{-1} reflecting the presence of an ester carbonyl. The nmr spectrum proved to be easily interpretable. Besides the triplet and quartet absorptions characteristic of an ethoxyl residue, it indicates the presence of two *N*-methyl groups, a methylenedioxy function, and two aromatic proton singlets, as expected for structure **22**.

To prove conclusively the structure of the new ester **22**, the known quaternary salt hydrastinine iodide (**24**)[4] was treated with benzyl chloroformate in the presence of aqueous sodium hydroxide. The resulting aldehydo urethan **25**, obtained in 65% yield, was efficiently reduced with lithium aluminum hydride in THF to the amino alcohol **26**. Oxidation of this material with pyridinium chlorochromate provided a 30% yield of the amino aldehyde **27** previously known as a degradation product of the alkaloid cryptopleurospermine (28).[5] Acid permanganate oxidation of **27**, immediately followed by esterification with absolute ethanol in the presence of thionyl chloride and sulfuric acid, gave rise to fumariflorine ethyl ester (**22**), identical with the material obtained from the isolation procedure.

To place fumariflorine within its proper biogenetic context, it is necessary first to note the prevalence of phthalideisoquinolines in the plant, namely species **5**–**9**, **16**, and **21**. A possible metabolic sequence in *F. parviflora*, therefore, must be such that the classical type phthalideisoquinolines such as (+)-α-hydrastine (**16**) or (+)-bicuculline (**5**) are initially *N*-methylated to their quaternary analogs. These salts undergo Hofmann elimination to supply phthalideisoquinolines with an open ring B, *e.g.*, *N*-methylhydrasteine (**6**) or its methylenedioxy analog **6a**. Finally, **6** or **6a**, or closely related alkaloids such as fumaridine (**8**) or fumaramine (**9**), can undergo oxidative cleavage to the amino acid fumariflorine (**23**). Since nature lacks an efficient mechanism for *O*-ethylation with the result that ethyl esters among alkaloids are unknown, and since ethanol was used during the extraction process, it is very likely that the true natural product is the amino acid fumariflorine (**23**), rather than its isolated ethyl ester **22**.

Since fumariflorine (**23**) is appreciably different in its structural features from such phthalideisoquinolines as **5**–**9**, **16**, and **21**, it is pertinent to consider it as the first representative of a new but small group of isoquinoline-derived alkaloids, namely the o-(β-dimethylaminoethyl)benzoic acids. Given that the new phthalideisoquinoline alkaloid fumaramidine (**21**) is present in *F. parviflora* and that other phthalideisoquinoline alkaloids such as corlumine, cordrastine, and adlumine are known to incorporate two methoxyl groups in ring A, it is likely that an analog of fumariflorine (**23**) yet to be found in nature is the amino acid **29**. The isolation and characterization of fumariflorine ethyl ester (**22**) has thus provided us with a new insight into the plant catabolism of phthalideisoquinoline alkaloids.

[4]Hydrastinine chloride is available from the Aldrich Chemical Co.

[5]For a listing of the spirobenzylisoquinoline alkaloids together with their physical constants and spectral data, see R. M. Preisner and M. Shamma, *J. Natural Products*, **43**, 305 (1980).

It is worth noting at this stage that the known simple isoquinolone alkaloid noroxyhydrastinine (**19**) is also present in *F. parviflora*. No studies using labeled precursors have been carried out to date to determine the biogenetic origin of the isoquinolones (6). A rational hypothesis, however, is that noroxyhydrastinine could derive in the plant from a number of sources. It is known, for example, that *in vitro* potassium permanganate oxidation of tetrahydroprotoberberines yields isoquinolones (6), and a parallel oxidation could take place in a living system. Alternatively, isoquinolones could be formed in the plant by the oxidation of tetrahydrobenzylisoquinolines. Yet another logical biogenetic route to noroxyhydrastinine (**19**) would be from a phthalideisoquinoline such as (+)-α-hydrastine (16). The sequence from (+)-α-hydrastine would involve initial *N*-demethylation to a norphthalideisoquinoline, which would very readily suffer oxidation to **19**. This route from (+)-α-hydrastine (**16**) would then represent an alternate catabolic pathway for the phthalideisoquinoline alkaloids.

Turning now to parviflorine (**30**), the third and by far the most polar of the new alkaloids found in the present study, it was quickly realized that this compound, $C_{26}H_{29}NO_{10}$, ν max (KBr) 1700 and 3390 cm^{-1}, readily affords tetraacetate derivative **31** upon treatment with acetic anhydride in pyridine, consonant with a sugar appendage in the alkaloid. Additionally, the presence of a ketone rather

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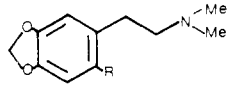
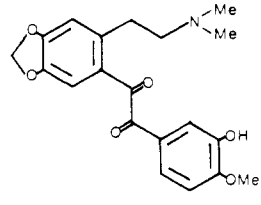


26, R = CH_2OH
27, R = CHO



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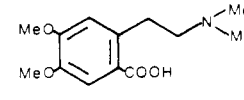

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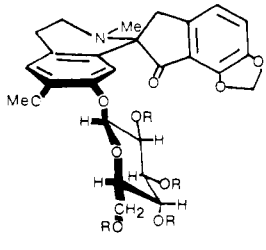
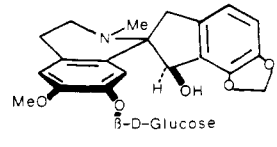
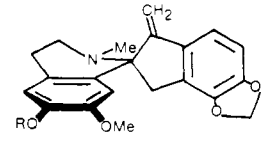


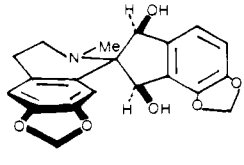
30, R = H
31, R = Ac



30a



32, R = H
33, R = Me



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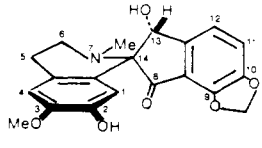

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than an ester carbonyl was indicated through reduction of the alkaloid with sodium borohydride to provide dihydroparviflorine (**30a**). Finally, hydrolysis of parviflorine (**30**) with 3N sulfuric acid gave, following work-up, the spirobenzylisoquinoline (+)-parfumine (14) as well as D-glucose (5).

The stereochemistry of the anomeric center in parviflorine was assigned on the basis of Klyne's rule (7) and was further supported by nmr spectral data. The molecular rotation of parviflorine (+5°) should be nearly equal to the sum of the molecular rotation of the aglycone parfumine (+64°) and that for either α-methyl-D-glucopyranoside (+309°) or for β-methyl-D-glucopyranoside (−66°). Since the sum of −2° obtained in the β-case is much closer to the required value of +5° than the sum of +373° derived from the α- case, it follows that parviflorine (**30**) is a β-D-glucoside. Parviflorine (**30**) thus corresponds to (+)-parfumine-β-D-glucoside.

Further support for the β-anomeric stereochemistry of parviflorine comes from the nmr pyridine-d_5 spectrum of the alkaloid. The spin-spin coupling constant for the anomeric proton resonance located at δ5.35 is 7.3 Hz. This relatively large value is consonant with a trans diaxial relationship between the anomeric hydrogen and the hydrogen on the adjacent carbon atom in the sugar moiety as indicated in expression **30**.

The only spirobenzylisoquinoline alkaloids whose absolute configuration had been established prior to the present work were (+)-ochotensine (**32**), ochotensimine (**33**), (+)-ochrobirine (**34**) and (+)-fumariline (**13**) (8, 9). In each case, the cd curve of the alkaloid or of its dihydro derivative had shown a positive Davydov split, so the aromatic chirality rule indicated the absolute configuration shown in expressions **13** and **32–34** (8). We have now recorded the cd curve for dihydroparfumine, the sodium borohydride reduction product of (+)-parfumine (14). This compound corresponds in all respects to the known alkaloid fumaritine (**17**). A positive Davydov split is evidenced between 277 and 294 nm, so the absolute configuration of **17** is identical with that of the spirobenzylisoquinolines previously studied. It follows that (+)-parfumine (**14**) and the chemically related (+)-parfumidine (**15**) also possess the same absolute configuration. The C–14 chirality indicated in expressions **13–15**, **17**, and **30–33** thus seems to be prevalent among the spirobenzylisoquinolines.[5]

The spirobenzylisoquinoline alkaloids are found almost exclusively within the plant genera *Fumaria* and *Corydalis* belonging to the family Fumariaceae.[5] An important generalization can at this stage be drawn between the plant source and the oxygenation pattern of ring C. The genus *Fumaria* yields spirobenzylisoquinolines bearing only one oxygenated substituent in ring C in the form of an alcohol, an acetate, a methoxyl ether or a ketone located at C–8. On the other hand, those bases originating from *Corydalis* species possess two oxygenated substituents in ring C, usually in the form of two alcohols or an alcohol plus a ketone. In the latter case, the alcohol will be at C–8 and the ketone at C–13. An apparent exception to this rule among the thirty alkaloids presently known is fumarofine (35), which occurs in *Fumaria* species yet incorporates a ketone at C–8 and an alcohol at C–13.

The isolation and characterization of parviflorine (**30**) is also of particular interest since it is only the sixth isoquinoline alkaloid out of the about seven hundred presently known that incorporates a glycosidic residue. The other

[7]Compound **27** has been previously prepared by a similar route, see M. D. Rozwadowska, *Bull. Acad. Pol. Sci.*, **19**, 673 (1971); *Chem. Abstr.*, **76**, 99480k (1972).

recognized glycosidic isoquinoline alkaloids are the simple tetrahydroisoquinoline pterocereine, the benzylisoquinolines latericine and veronamine, the rhoeadine isorhoeagenine-α-D-glucoside, and the Ipecac base ipecoside (6).

EXPERIMENTAL[6]

INITIAL EXTRACTION AND FRACTIONATION PROCEDURE.—The dried ethanolic extract from 8 kg of the whole powdered plant material was extracted with 2.1 liters of 5% hydrochloric acid, and the aqueous layer was filtered from the large amount of chlorophyll and other insoluble matter. A further extraction of the insoluble matter was then carried out with another 1.4 liters of 5% hydrochloric acid. Following filtration, the combined aqueous extracts were exhaustively extracted with chloroform. Removal of the organic solvent gave 35 g of Extract A. The acidic aqueous fraction was made alkaline (pH 8) with ammonium hydroxide and reextracted with chloroform. Removal of the organic solvent furnished 12 g of Extract B.

FRACTIONATION OF EXTRACT A.—Extract A was chromatographed on a column of silica gel in chloroform. One half liter fractions, 243 in number, were collected by elution first with chloroform and then with increasing proportions of methanol in chloroform. Based on their tlc patterns, the fractions were combined into seven major groups labeled A-I to A-VII.

FRACTIONATION OF EXTRACT B.—Extract B was chromatographed as above; 155 fractions were collected. These were combined into five major groups labeled B-I to B-V.

STYLOPINE (**2**) AND FUMARILINE (**13**).—Preparative tlc of group A-I (1.1 g) in benzene-methanol (80:20) afforded two alkaloids, stylopine (3.9 mg) and fumariline (170 mg) with R_f 0.57 and 0.38, respectively. Stylopine nmr δ5.93 (2H, s, OCH_2O), 5.95 (2H, apparent d, J=5.3 Hz, OCH_2O), 6.60 (1H, s, ArH), 6.65 (1H, d, J=8.0 Hz, ArH), 6.69 (1H, d, J=8.0 Hz, ArH), 6.74 (1H, s, ArH); the material isolated was identical with an authentic sample. Fumariline, nmr data table 1; ν max ($CHCl_3$) 1715 cm^{-1}, mass spectrum m/e 351 (M^+, $C_{20}H_{17}NO_5$), 336, 322 (base), 293, 292, 264 and 175.5.

TABLE 1. Nmr resonances of spirobenzylisoquinolines at 200 MHz (FT).

Compound	*N*-Methyl	*O*-Methyls	Methylene-dioxy	Aromatic Hydrogens			
		C-2 C-3 (OCH_2O)	C-9, 10	H-1	H-4	H-11	H-12
Fumariline (**13**)	δ 2.35	(5.84)	6.16	6.18	6.57	7.12 (7.7 Hz)	6.91 (7.7 Hz)
Parfumidine (**15**)	2.35	3.59 3.84	6.17	6.18	6.60	7.13 (7.9 Hz)	6.93 (7.9 Hz)
Parfumine (**14**)	2.37	— 3.85	6.16	6.30	6.58	7.11 (7.9 Hz)	6.90 (7.9 Hz)
Fumaritine (**17**)	2.40	— 3.86	5.96[c]	6.48	6.61	6.78 (7.7 Hz)	6.70 (7.7 Hz)
Parviflorine (**30**)[a]	2.45	— 4.67	6.13[d]	7.05	6.73	7.15 (7.9 Hz)	6.89 (7.9 Hz)
Parviflorine tetraacetate (**31**)[b]	2.37	— 3.78	6.20[e]	6.45	6.63	7.10 (7.9 Hz)	6.91 (7.9 Hz)

[a]This spectrum was obtained in pyridine-d_5. All other spectra are in $CDCl_3$.

[b]The four acetyl proton singlets are at δ1.99, 2.00, 2.01 and 2.04.

[c]Apparent doublet, J=4.6 Hz.

[d]Apparent doublet, J=7.2 Hz.

[e]Apparent doublet, J=5.4 Hz.

PARFUMIDINE (**15**).—Fractionation of group A-II (720 mg) by preparative tlc in benzene-methanol (80:20) yielded a pale yellow oil (57 mg); nmr data table 1; mass spectrum m/e 367 (M^+, $C_{21}H_{21}NO_5$), 352, 338 (base), 325, 324 and 308.

[6]Melting points are uncorrected. All nmr data were obtained with a Bruker 200 MHz Supercon (FT) spectrometer, except for the spectra for compounds **25**, **26** and **27** where a Varian EM-360 spectrometer was used. $CDCl_3$ was the usual nmr solvent, and TMS was the internal standard. The nmr spectra at 200 MHz in $CDCl_3$, unless indicated otherwise, for some of the phthalideisoquinolines and the spirobenzylisoquinolines discussed in this paper have been summarized in tables 1 and 2. Mass spectra were collected on an AEI MS-902 instrument. The circular dichroism measurements were done on a JASCO-20 spectropolarimeter. All tlc was on Merck silica gel F-254 glass plates. The relative R_f values for the isoquinoline alkaloids isolated and some of their derivatives have been listed in table 3, while additional R_f values are given below.

PARFUMINE (**14**), (+)BICUCULLINE (**5**) AND (+)-α-HYDRASTINE (**16**).—Preparative tlc of a 200 mg fraction of group A-III (5.7 g) in benzene-methanol (80:20) provided two major fractions with R_f 0.54 and 0.30. The alkaloid with lower R_f was further purified by tlc and identified as parfumine (22 mg), nmr data table 1; ν max ($CHCl_3$) 1710 cm^{-1}; mass spectrum *m/e* 353(M^+, $C_{20}H_{19}NO_5$), 338, 325, 324 (base) and 308; cd $\Delta\epsilon_{nm}$(MeOH) $+1.14_{355}$, -1.76_{295}, -6.36_{259} and $+1.18_{239}$. The high R_f fraction was subjected to tlc in benzene-methanol (90:10) twice, after which a separation was achieved; two alkaloids, **5** (3 mg) and **16** (2.8 mg), were obtained and identified by direct comparison with authentic samples (2).

N-METHYLHYDRASTEINE (**6**) AND FUMARITINE (**17**).—Group A-IV (2.1 g) showed intense greenish-blue fluorescence under long wavelength uv light. A portion of this fraction, amounting to 500 mg, was dissolved in chloroform and reprecipitated by the addition of benzene. The precipitate gave a negative alkaloidal test and was discarded. The filtrate was dried (370 mg) and then subjected to tlc with chloroform-methanol (95:5). The plates were allowed to stand in the developing medium for some 5 hours. The major uv fluorescent band of higher R_f was identified as *N*-methylhydrasteine (5 mg) by comparison with an authentic sample; nmr data table 2 (2). The minor fraction of lower R_f on further purification yielded fumaritine (3.2 mg), nmr data table 1, mass spectrum *m/e* 355 (M^+, $C_{20}H_{21}NO_5$), 340, 324 and 192 (base); cd $\Delta\epsilon_{nm}$(MeOH) $+8.96_{294}$, -2.68_{277} and $+3.58_{236}$.

ISOBOLDINE (**18**).—The major component of group A-V (700 mg) was found to be *N*-methylhydrasteine (238 mg). However, upon preparative tlc in chloroform-diethylamine (95:5), a small quantity (1.3 mg) of isoboldine was obtained, which was characterized by comparison with an authentic sample.[3]

PROTOPINE (**10**).—Preparative tlc of group A-VI (1 g) in chloroform-diethylamine (95:5) provided protopine (110 mg), identified by comparison with an authentic sample.[3]

COPTISINE CHLORIDE (**3**).—Group A-VIII (1.3 g) deposited brownish yellow crystals (45 mg) on standing. These were recrystallized from methanol and were identified by comparison with an authentic sample.[3]

NOROXYHYDRASTININE (**19**).—The major constituent of group B-I (330 mg) was parfumine (**14**) (68 mg). But a minor constituent of low R_f was separated by preparative tlc with chloroform-diethylamine (95:5) and identified as **19** (8.5 mg) by comparison with an authentic sample.[3]

PROTOPINE (**10**) and ISOBOLDINE (**18**).—Some of the fractions making up group B-II (500 mg) crystallized in methanol. The crystals were collected and identified as protopine (200 mg) by comparison with an authentic sample. Tlc of the alkaloids in the remaining mother liquor with chloroform-diethylamine (95:5) provided isoboldine (39 mg).[3]

FUMARAMINE (**9**) AND FUMARAMIDINE (**21**).—When the combined fractions of group B-III (708 mg) were dissolved in methanol and the solution kept overnight, crystals of protopine (68 mg) settled down and were separated. The alkaloids of the mother liquor were subjected to tlc on 2 mm thick plates with chloroform-acetone-diethylamine (5:4:1). The major fraction, R_f 0.44, was further fractionated on 0.5 mm plates in the same solvent system; two major bands appeared. The fast moving band exhibited no fluorescence under uv light, while the slow moving band gave a blue fluorescence and crystallized. Notwithstanding precipitation of these crystals, the slow moving band was redissolved and further fractionated on 0.25 mm thick plates; the system used was benzene-chloroform-diethylamine (5:4:1). Two fractions which showed very close R_f values were thus separated. The fraction with the higher R_f was identified as fumaramine (6.5 mg) by direct comparison with a sample derived from bicuculline (4); nmr data table 2. The low R_f fraction proved to be fumaramidine (2.5 mg), nmr data table 2; mass spectrum *m/e* 396 (M^+, $C_{22}H_{24}N_2O_5$), 220 and 58 (base).

FUMARIFLORINE ETHYL ESTER (**22**).—The fast moving band from group B-III, which showed no uv fluorescence, was further purified by tlc in chloroform-diethylamine (95:5). Colorless, waxy **22** was thus obtained (18 mg), R_f 0.44; nmr δ1.38 (3H, t, J=7 Hz, CH_3CH_2), 2.34 (6H, s, 2xNCH_3), 2.53 (2H, m, CH_2N), 3.12 (2H, m, $ArCH_2$), 4.33 (2H, q, J=7 Hz, CH_3CH_2), 5.99 (2H, s, OCH_2O), 6.74 (1H, s, H-3), and 7.39 (1H, s, H-6); λ max (EtOH) 218, 262 and 292 (log ε 4.45, 3.87 and 3.78); ν max ($CHCl_3$) 1710 cm^{-1}; mass spectrum *m/e* 265 (M^+, $C_{14}H_{19}NO_4$), 220 ($M-OC_2H_5$), 134 $(C_8H_6O_2)^+$ and 58 $(CH_2=N(CH_3)_2)^+$ (base); high resolution mass spectrum *m/e* 265.1306 (calcd. for M^+ $C_{14}H_{19}NO_4$ *m/e* 265.1312).

PARVIFLORINE (**30**).—Concentration of the fractions comprising group B-IV (724 mg) furnished colorless crystals (70 mg), mp 230–232°, $[\alpha]^{27}D$ +1° (c 0.0124, MeOH); nmr data table 1; λ max (MeOH) 233, 260, 288 sh and 352 nm (log ε 4.50, 4.18, 3.70 and 3.66); ν max (KBr) 1700 and 3390 cm^{-1}; mass spectrum *m/e* 515 (M^+, $C_{26}H_{29}NO_{10}$), 353, 338, 325 and 324 (base); cd $\Delta\epsilon_{nm}$ (MeOH) $+1.94_{355}$, -4.62_{293}, -18.25_{261}, $+4.62_{240}$ and -4.38_{229}.

PARVIFLORINE TETRAACETATE (**31**).—A mixture of parviflorine (10 mg), acetic anhydride (2 ml), and pyridine (1 ml) was kept at room temperature for 10 hours. Excess reagent and

solvent were removed *in vacuo*. The residue crystallized from methanol (8.2 mg), mp 225–226°; nmr data table 1; ν max ($CHCl_3$) 1708 cm^{-1}; mass spectrum *m/e* 683 (M^+, $C_{34}H_{37}NO_{14}$), 352 and 324 (base).

DIHYDROPARVIFLORINE (**30a**).—Parviflorine (11 mg) was dissolved in methanol and stirred for 4 hours with excess sodium borohydride and six drops of 2N hydrochloric acid. The mixture was then made alkaline with ammonium hydroxide, and the solvent was removed *in vacuo*. The residue was exhaustively extracted with hot chloroform. Removal of the solvent left a white solid which was purified further by tlc in chloroform-methanol (80:20). The salient nmr spectral peaks of **30a** in pyridine-d_5 are at δ2.39 (3H, s, NCH_3), 3.62 (3H, s, OCH_3), 5.84 (2H, apparent d, J=9.8 Hz, OCH_2O), 6.72 (1H, d, J=7.8 Hz, ArH), and 6.82 (1H, d, J=7.8 Hz, ArH); λ max (MeOH) 260, 278 sh and 290 sh (log ϵ 3.94, 3.66 and 3.53); mass spectrum *m/e* 517 (M^+, $C_{26}H_{31}NO_{10}$), 355, 354, 340, 337 and 192 (base); cd $\Delta\epsilon_{nm}$ (MeOH) $+4.87_{232}$, -1.16_{276}, $+1.16_{263}$ and $+4.6_{249}$.

HYDROLYSIS OF PARVIFLORINE (**30**).—Parviflorine (8 mg) was stirred with 3N H_2SO_4 (20 ml) at 70° for 12 hours. The solution was cooled, and barium carbonate was added. The barium salts were removed by repeated filtrations, and the clear solution was extracted with chloroform. Removal of the solvent from the chloroform layer afforded an oil (2.3 mg) identical in all respects with (+)-parfumine. The aqueous layer was evaporated to near dryness, and the residue was identified as D-glucose by paper chromatography with *n*-butanol-pyridine-water (9:5:4) (R_f 0.14) and also by tlc on a cellulose plate with *n*-butanol-acetic acid-water (6:2:2) (R_f 0.40).

FUMARIDINE (**8**).—Group B–V (700 mg) exhibited blue fluorescence under uv light. Repeated tlc in acetone-chloroform-diethylamine (5:4:1) and chloroform-diethylamine (95:5) afforded a blue fluorescent compound under uv which was identified as fumaridine (6 mg) by comparison with an authentic sample derived from (−)-β-hydrastine (4); nmr data table 2.

TABLE 2. Nmr resonances of open chain phthalideisoquinolines at 200 MHz (FT).[a]

	N-Methyl	*O*-Methyls	*O*-Methyls	Aromatic Hydrogens				
		C-2 C-3 (OCH_2O)	C-9 C-10 (OCH_2O)	H-1	H-4	H-11	H-12	H-14
N-Methylhydrasteine (**6**)	δ2.27	(5.97)	4.15 3.95	6.47	6.70	7.50 (8.4 Hz)	7.29 (8.5 Hz)	7.71
Fumaramine (**9**)	2.29	(5.98)	(6.19)	6.44	6.77	7.30 (8.1 Hz)	7.07 (8.1 Hz)	6.84
Fumaramidine (**21**)	2.31	3.89 3.92	(6.20)	6.49	6.79	7.32 (8.1 Hz)	7.08 (8.1 Hz)	6.84
Fumaridine (**8**)	2.27	(5.98)	4.12 3.95	6.41	6.77	7.46 (8.2 Hz)	7.19 (8.4 Hz)	6.85

[a]All spectra were obtained in $CDCl_3$.

N-CARBOBENZOXY-N-METHYL-2-FORMYL-4,5-METHYLENEDIOXY-β-PHENETHYLAMINE (**25**).—A suspension of 6,7-methylenedioxy-*N*-methyl-3,4-dihydroisoquinolinium iodide (**24**) (3.0 g) in ether (120 ml), water (10 ml) and 10% aqueous sodium hydroxide (12 ml) was stirred, and benzyl chloroformate (2 ml) was added. After six hours of continuous stirring, 6 ml of 10% aqueous sodium hydroxide and 2 ml of benzyl chloroformate were added, and stirring was continued. After another two hours, 12 ml of 10% aqueous sodium hydroxide and 4 ml of benzyl chloroformate were added, and stirring was continued for four hours. A further 2 ml of aqueous sodium hydroxide and 2 ml of ethyl chloroformate were added, and the reaction mixture was stirred overnight. The ether layer was separated, and the aqueous layer was extracted twice with ether. Removal of the solvent from the combined ether extracts yielded an oil which was chromatographed on a silica gel column with benzene as the eluent. The material thus collected proved to be unreacted benzyl chloroformate. Further elution of the column with 20% methanol in chloroform gave rise to urethan **25** as a colorless oil which crystallized on standing (2.1 g, 65%), mp 88–89°; nmr δ2.87 (3H, s, NCH_3), 5.02 (2H, s, OCH_2Ph), 5.95 (2H, s, OCH_2O), 6.49 (1H, s, H-6), 6.68 (1H, s, H-3), 7.30 (5H, s, benzylic H), 10.01 (1H, s, CHO); ν max ($CHCl_3$) 1690 cm^{-1} (br); mass spectrum *m/e* 341 (M^+, $C_{19}H_{19}NO_5$), 323, 206, 176, 163, 134 and 91 (base).

2-(β-DIMETHYLAMINO)ETHYL-4,5-METHYLENEDIOXYBENZYL ALCOHOL (**26**).—Urethan **25** (1.8 g) was reduced with lithium aluminum hydride (650 mg) in THF. Work-up of the mixture gave an oily residue which was dissolved in chloroform and extracted with 2N hydrochloric acid. The acidic extract was made alkaline with 10% sodium hydroxide solution and was extracted with chloroform. Drying and removal of the organic solvent provided a colorless oil which crystallized at room temperature, 1.04 g (89%), mp 69–70°; nmr δ2.18 (6H, s, NCH_3), 4.40 (2H, s, CH_2OH), 5.82 (2H, s, OCH_2O), 6.58 (1H, s, H-3) and 6.74 (1H, s, H-6); mass spectrum *m/e* 223 (M^+, $C_{12}H_{17}NO_3$), 163, 148 and 58 (base).

2-(β-DIMETHYLAMINO)ETHYL-4,5-METHYLENEDIOXYBENZALDEHYDE (**27**).—A solution of alcohol **26** (300 mg) in methylene chloride (3 ml) was added rapidly to a stirred slurry of pyridinium chlorochromate (450 mg) in methylene chloride (3 ml). The mixture was stirred for 90 minutes, diluted with methylene chloride (20 ml), and filtered. The filtrate was washed with ammonium hydroxide and dried over sodium sulfate. Removal of the solvent and tlc of the residue in benzene-chloroform-diethylamine (5:4:1) furnished a light colored viscous oil (90 mg, 30%); nmr δ2.26 (6H, s, NCH_3), 5.95 (2H, s, OCH_2O), 6.68 (1H, s, H-3), 7.22 (1H, s, H-6) and 10.05 (1H, s, CHO); ν max ($CHCl_3$) 1690 cm^{-1}; mass spectrum *m/e* 221 (M^+, $C_{12}H_{15}NO_3$), 177, 163, 147, 135 and 58 (base).[6]

FUMARIFLORINE ETHYL ESTER (**22**).—A solution of $KMnO_4$ (60 mg) in water (3 ml) and acetone (3 ml) was added dropwise in 45 minutes at room temperature to a continuously stirred solution of **27** (88 mg) in acetone (2 ml), water (2 ml) and six drops of 2N HCl. The reaction mixture was stirred for another 15 minutes and filtered, and the solvent was then evaporated. The dry residue was dissolved in hot ethanol (15 ml); four drops of conc. sulfuric acid and 0.75 ml of thionyl chloride were cautiously added. The solution was refluxed for two hours. The reaction mixture was then cooled, diluted with water, made alkaline with ammonium hydroxide, and extracted with chloroform. After removal of the solvent, the residue when subjected to tlc in benzene-chloroform-diethylamine (5:4:1) afforded 12 mg (11%) of fumariflorine ethyl ester, identical with material obtained from the plant isolation.

TABLE 3. R_f Values of alkaloids and some of their derivatives.

In chloroform-diethylamine (95:6)	
Fumaritine (**17**)	0.42
N-Methylhydrasteine (**6**)	0.40
Parfumidine (**15**)	0.61
Parviflorine tetraacetate (**31**)	0.62
Fumaridine (**8**)	0.51
Noroxyhydrastinine (**19**)	0.30
Isoboldine (**18**)	0.14
In chloroform-methanol (80:20)	
Dihydroparviflorine (**30a**)	0.10
Parviflorine (**30**)	0.27
Parviflorine tetraacetate (**31**)	0.64
Coptisine chloride (**3**)	0.16
In benzene-chloroform-diethylamine (5:4:1)	
Fumaramine (**9**)	0.42
Fumaramidine (**21**)	0.37
In chloroform-methanol (95:5)	
N-Methylhydrasteine (**6**)	0.16
Fumaritine (**17**)	0.16
Parfumine (**14**)	0.34

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