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Alkaloids of *Cryptocarya phyllostemon*

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Abstract

The known alkaloids (–)-antofine (1), dehydroantofine (5), (–)-cryptowoline (6), (–)-cryptowolidine (7), and (–)-cryptowolinol (8), were isolated from the New Caledonian lauraceous plant *Cryptocarya phyllostemon*, together with five new bases: two secophenanthroindolizidines, (–)-phyllostemine (2) and (–)-phyllosteminine (3), one pyrrolidinylacetophenone, (–)-phyllostone (4), and two quaternary tetrahydrobenzylisoquinolines, (+)-phyllocryptine (9) and (+)-phyllocryptonine (10). Chemical and spectroscopic methods were used for identification and structural investigation.

A synthesis of phyllocryptonine has permitted its stereostructure to be determined.

Introduction

The genus *Cryptocarya* (Lauraceae), which includes about 350 species, belongs to the subfamily Lauroideae, tribe *Cryptocaryeae*, and subtribe *Cryptocaryinae*.[1] This pantropical genus, which is wide-spread especially in Malaysia and New Guinea, is represented in New Caledonia by 19 species.[2] In the course of a study embracing several of the New Caledonian species, we have examined the alkaloid content of one of these, *C. phyllostemon* Kost., whose chemical constituents to our knowledge have not been previously investigated.

Cryptocarya phyllostemon is a small tree endemic in New Caledonia which grows to a height of 2–8 m, with lanceolate leaves (7 by 2 cm) and bluish conical fruit (12 by 27 mm). This species was described in 1974 by Kostermans; it is very close to another species, *C. oubatchensis* Schlechter with which it had previously been confused, but it is distinguished from the latter in particular by the acuminate shape of the leaves and the pilosity of the twigs.

[1] Kostermans, A. J. G. H., *Reinwardtia*, 1957, 4(2), 193.
[2] Kostermans, A. J. G. H., in 'Flore de la Nouvelle Calédonie et Dépendances' (Eds A. Aubréville and J. F. Leroy) Vol. 5 (Museum National d'Histoire Naturelle: Paris 1974).

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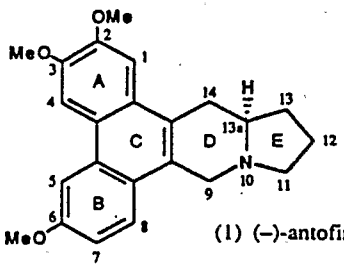
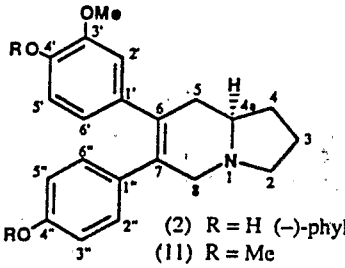
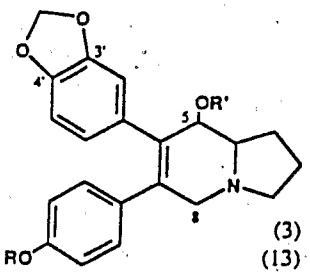


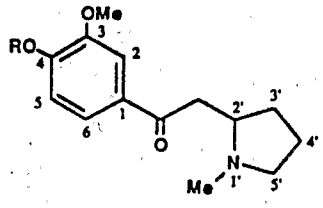
(1) (–)-antofine



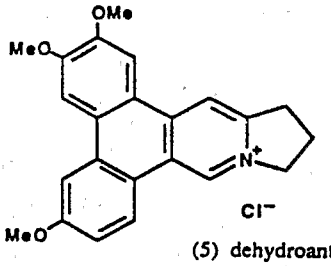
(2) R = H (–)-phyllostemine
(11) R = Me



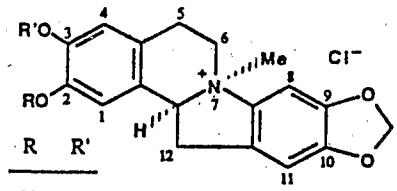
	R	R'	
(3)	H	H	(–)-phyllosteminine
(13)	Me	H	
(14)	Me	Ac	



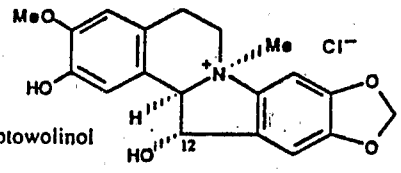
(4) R = H (–)-phyllostone
(16) R = Me



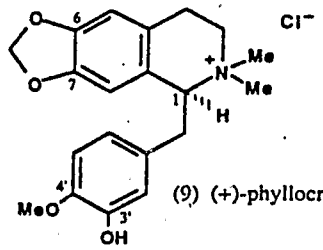
(5) dehydroantofine



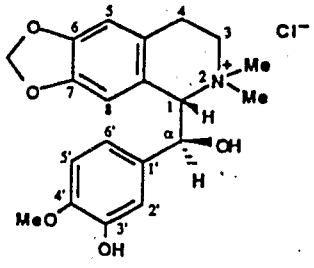
	R	R'	
(6)	H	Me	(–)-cryptowoline
(7)	Me	H	(–)-cryptowolidine



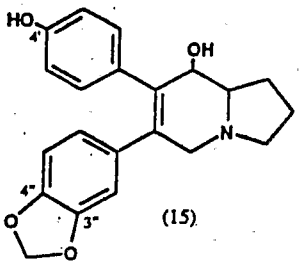
(8) (–)-cryptowolinol



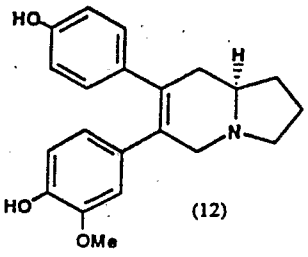
(9) (+)-phyllocryptine



(10) (+)-phyllocryptonine



(15)



(12)

Results and Discussion

Our studies have been carried out on two samples of plant material, one consisting of leaves, twigs, roots and fruit and the other of stem bark, which were collected at different times in New Caledonia. The total alkaloids, extracted by the usual methods, consisted for the most part of quaternary bases (yield 4·5%) accompanied by a small quantity of tertiary alkaloids (yield 0·15–0·6% according to sample). By repeated chromatography on silica gel columns followed by purification by crystallization, or p.t.l.c. on silica gel, ten alkaloids have been isolated in all, of which five are new.

The main tertiary alkaloid proved to be a phenanthroindolizidine which was identified as (–)-antofine (1). Three other tertiary alkaloids were isolated: two new secophenanthroindolizidines (septicine type) named (–)-phyllostemine (2) and (–)-phyllosteminine (3), and a new pyrrolidinylacetophenone for which the name (–)-phyllostone (4) is proposed. The quaternary ammonium bases belong to three structural types: the phenanthroindolizidine dehydroantofine (5); three dibenzopyrrocolines, (–)-cryptowoline (6), (–)-cryptowolidine (7) and (–)-cryptowolinol (8); and two new benzyltetrahydroisoquinolines, which have been named (+)-phyllocryptine (9) and (+)-phyllocryptonine (10). The alkaloids described previously were identified by their physical constants and spectroscopic data, and by comparison with authentic samples. The structures of the new alkaloids have been established by chemical and spectroscopic means, and in the case of phyllocryptonine the structure has been confirmed by synthesis.

The presence of seven of these alkaloids in *Cryptocarya phyllostemon* has been reported in a preliminary communication.[3] It may be noted that alkaloids (2)–(5) were isolated only from the first sample, and (6)–(8) only from the second, and that only three of the alkaloids [(1), (9) and (10)] were found in both the plant samples that were examined.

Phenanthroindolizidines

That alkaloid (1) belonged to the phenanthroindolizidine group was indicated by its mass spectrum: apart from a molecular peak at *m/z* 363 corresponding to the formula $C_{23}H_{25}NO_3$, the mass spectrum had a base peak at *m/z* 294 (M−69) and another peak at *m/z* 69. These fragments are characteristic of phenanthroindolizidines, which undergo a cleavage by a retro Diels–Alder type of mechanism with loss of ring E in the form of 1,2-dehydropyrrolidine.[4] The u.v. spectrum is likewise in accord with the presence of a phenanthrene chromophore. The molecular formula of (1) together with its ^{1}H n.m.r. spectrum indicates the presence of three methoxy groups; for biogenetic reasons[5,6] these are located either at C2, C3 and C6 (antofine), or C3, C6 and C7 (desoxytylophorinine or desoxypergularinine). The first of these hypotheses was confirmed by the observation of nuclear Overhauser effects in an ^{1}H n.m.r. spectrum recorded in $CDCl_3$ at 270 MHz: irradiation of one of the protons at

[3] Bick, I. R. C., Sinchai, W., Sévenet, T., Ranaivo, A., Niéto, M., and Cavé, A., *Planta Med.*, 1980, **39**, 205.
[4] Pailer, M., and Streicher, W., *Monatsh. Chem.*, 1965, **96**, 1094.
[5] Mulshandani, N. B., Iyer, S. S., and Badheka, L. P., *Phytochemistry*, 1976, **15**, 1697.
[6] Bhakuni, D. S., and Mangla, V. K., *Tetrahedron*, 1981, **37**, 401.

C9 resonating at δ 4·75 (doublet) produces an enhancement in intensity of an aromatic proton signal which forms a doublet (J_o 9 Hz) at δ 7·82. This can only be the proton at C8, and it is clear from its coupling constant that C7 is unsubstituted, so that the three methoxyls can be assigned unambiguously to C2, C3 and C6. The identity of alkaloid (1) with (–)-antofine (configuration 13a-*R*) was confirmed by direct comparison with an authentic specimen.

The quaternary base (5) was precipitated as reineckate with other water-soluble alkaloids, then converted into the chloride and purified by crystallization of the sparingly soluble perchlorate salt, and finally reconverted into the chloride. The mass spectrum of this salt showed a molecular cation with three hydrogens less than the molecular ion of antofine (1), and its u.v. spectrum was likewise similar to the antofine spectrum. Borohydride reduction of alkaloid (5) gave a product identical with antofine (1), and the perchlorate of alkaloid (5) likewise proved identical with the perchlorate salt formed on oxidation of antofine (1) with mercuric acetate. Alkaloid (5) is thus shown to be dehydroantofine.

(–)-Antofine (1) and dehydroantofine (5) are described here for the first time in a lauraceous species. Antofine has been previously isolated from only two plant families,[7-9] Asclepiadaceae (genera *Antitoxicum, Cynanchum, Pergularia, Tylophora*) and Moraceae *(Ficus septica).* Dehydroantofine is reported here for the first time as a natural product. Some doubt has been expressed[10] as to whether dehydrotylophorine, a close analogue of dehydroantofine, occurs as such in the living plant or whether it is an artefact formed during the process of extraction and isolation; the same ambiguity exists as far as dehydroantofine (5) is concerned.

Secophenanthroindolizidines (Septicine-Type Alkaloids)

Phyllostemine (2) and phyllosteminine (3), two new representatives of this small group which is biogenetically related to the phenanthroindolizidines, were isolated from *Cryptocarya phyllostemon.*

The mass spectrum of (–)-phyllostemine revealed a strong molecular ion at *m/z* 337 and a base peak at *m/z* 268 (M–69); high resolution showed that the molecular ion corresponded to the formula $C_{21}H_{23}NO_3$, and that the loss was due to a fragment C_4H_7N, which strongly suggested the presence of an indolizidine nucleus. The appearance of a prominent *m/z* 70 ion (protonated 1,2-dehydropyrrolidine arising from hydrogen transfer to the pyrroline fragment after retro Diels–Alder type cleavage) was also in accord with this inference. The ^{1}H n.m.r. spectrum of phyllostemine revealed the absence of any *N*-methyl group and the presence of one methoxy group at δ 3·54; after methylation with diazomethane, signals corresponding to two extra methoxyls appeared at δ 3·75 and 3·83, and this *O,O*-dimethyl derivative (11) could be formulated as $C_{23}H_{27}NO_3$, *i.e.* two more hydrogen atoms than in antofine (1). These data

[7] Bick, I. R. C., and Sinchai, W., in 'The Alkaloids' (Ed. R. G. A. Rodrigo) Vol. 19, p. 193 (Academic Press: New York 1981).
[8] Gellert, E., *J. Nat. Prod.*, 1982, 45, 50.
[9] Gellert, E., in 'Alkaloids: Chemical and Biological Perspectives' (Ed. S. W. Pelletier) Vol. 5, p. 55 (Wiley-Interscience: New York 1987).
[10] Govindachari, T. R., Wiswanathan, N., Radhakrishnan, J., Charubala, R., Nityananda Rao, N., and Pai, B. R., *Indian J. Chem.*, 1973, **11**, 1215.

can be interpreted in terms of a tertiary secophenanthroindolizidine with one methoxy and two hydroxy groups.

Phyllostemine gave a negative test with Gibbs reagent, and the phenolic groups must in consequence be *para* substituted; this suggested one of two structures, (2) or (12), in which the methoxyl is located at C 3′ or C 3″, in accord with its upfield shift in the ^{1}H n.m.r. spectrum. The other n.m.r. data for phyllostemine are also in general agreement with these alternative structures, of which the former, (2), has the same oxygenation pattern as antofine (1) and is preferred as the more likely structure for phyllostemine on biogenetic grounds. Moreover, julandine, a closely analogous secophenanthroquinolizidine, has three methoxy groups in corresponding positions to those postulated for the oxy functions of phyllostemine, and the chemical shifts quoted for the methoxyl and aromatic protons in the ^{1}H n.m.r. spectrum of julandine[11] correspond closely with those observed for *O,O*-dimethylphyllostemine (11). Structure (2) has thus been assigned to (–)-phyllostemine, and a 4a-*R* configuration is attributed to it on the basis of its negative specific rotation.

Phyllosteminine was isolated as colourless crystals from chloroform; its molecular formula, $C_{21}H_{21}NO_4$, was established by high-resolution mass spectrometry. The mass spectrum showed a weak molecular ion at *m/z* 351, and a base peak at *m/z* 69 as well as a prominent peak at *m/z* 282 (M–69), which strongly suggested the presence of an indolizidine nucleus. The u.v. spectrum of phyllosteminine was similar to that of phyllostemine (2), and suggested a secophenanthroindolizidine structure. The presence of a phenolic hydroxy group was shown by a bathochromic shift in the u.v. spectrum on addition of alkali, and was confirmed by the formation of an *O*-methyl ether (13) with diazomethane. The alkaloid gave a negative test with Gibbs reagent, which indicated that the phenolic hydroxy group was in a *para*-substituted aromatic ring.

The ^{1}H n.m.r. spectrum of phyllosteminine was in general agreement with a secophenanthroindolizidine structure bearing one methylenedioxy substituent (two-proton singlet at δ 5·85), but no methoxy group. It showed absorptions corresponding to seven aromatic protons, and the presence of an alcoholic hydroxyl was suggested by a one-proton doublet at δ 4·47, J 8 Hz, which could be assigned to the CHOH proton. Moreover, acetylation of the *O*-methyl ether (13) afforded an acetate (14), in whose i.r. spectrum a carbonyl band appeared at 1730 cm^{-1}. The frequency indicated that the ester function was derived from an aliphatic hydroxy group, and this observation was confirmed by the presence of a three-proton singlet at δ 1·77 in the ^{1}H n.m.r. spectrum, corresponding to an alcoholic acetate.

The location of the alcoholic group in phyllosteminine was shown by its mass spectrum, in which a peak appeared at *m/z* 254, arising from the *m/z* 282 ion by elimination of carbon monoxide; likewise, the mass spectrum of the acetate ester (14) showed, besides the molecular ion at *m/z* 407, a base peak at *m/z* 296 which could be ascribed to the loss of a pyrroline residue followed by loss of ketene, and a prominent peak at *m/z* 347 corresponding to the loss of acetic acid through a McLafferty rearrangement. These fragmentations were indicative of the presence of a hydroxy group at C5 or C8 in the

[11] Hart, N. K., Johns, S. R., and Lamberton, J. A., *Aust. J. Chem.*, 1968, **21**, 2579.

indolizine residue of phyllosteminine.[7] However, the possibility of a C8 hydroxyl, adjacent to the nitrogen, could be ruled out, since phyllosteminine did not have the properties of a carbinolamine, and in particular showed no absorption around 400 nm in its u.v. spectrum.

From the spectroscopic data, two possible structures (3) or (15) may be written for phyllosteminine at this stage. A decision between these alternatives could be made in favour of structure (3), from an analysis of the ^{1}H n.m.r. data. The spectrum of phyllosteminine (270 MHz) shows a pair of doublets around δ 3·25 and 3·97 which can be assigned to the methylene protons attached to C8. As in the case of phyllostemine (2), they are not so strongly deshielded as the corresponding protons of antofine (1), probably because ring B is twisted out of plane to some extent. In the aromatic region of the spectrum, a double doublet corresponding to four protons in a *para*-disubstituted benzene ring appears; in the ^{1}H n.m.r. spectrum of the *O*-methyl derivative (13), a downfield shift of 0·11 ppm is observed for the protons *ortho* to the methoxyl. The remaining aromatic protons in the spectrum of the *O*-methyl derivative (13) exhibit a two-proton doublet around δ 6·70 and a broad singlet at δ 6·60, corresponding to the protons attached respectively to C5′, C6′ and C2′ in structure (3), or C5″, C6″ and C2″ in structure (15). The signals due to these three protons suffer an upfield shift of 0·11–0·21 ppm in the spectrum of (14), in which the alcoholic group has been acetylated; the pair of doublets due to the other four aromatic protons are unaffected by the acetylation. It is clear that the acetoxy group, in comparison to the hydroxyl, is exerting a shielding effect on the protons of the adjacent aromatic ring, which must be the ring bearing the methylenedioxy group and not the methoxy group, since the latter must be in the *para*-substituted ring. Phyllosteminine thus has structure (3), it is the first septicine-type alkaloid to be reported with a 5-hydroxy group.[9]

Pyrrolidinylacetophenone

The new alkaloid (–)-phyllostone was obtained as a colourless gum; its molecular formula, $C_{14}H_{19}NO_3$, was established by high-resolution spectrometry. Its i.r. spectrum showed an absorption band at 1655 cm^{-1}, indicative of a conjugated carbonyl. The u.v. spectrum suggested an acetophenone chromophore with a phenolic hydroxy substituent; evidence of the latter group resulted from the bathochromic shift produced by addition of alkali, and from the formation of an *O*-methyl ether (16) with diazomethane. The ^{1}H n.m.r. spectrum of phyllostone showed signals corresponding to three aromatic protons, which from their splitting patterns were in 1,2,4-positions relative to one another; furthermore, two three-proton singlets at δ 3·84 and 2·65 were assigned to a methoxy and an *N*-methyl group, respectively. The acetophenone part of the molecule bears methoxy and hydroxy substituents, of which the latter must be located *para* to the carbonyl group: phyllostone gives a negative test with Gibbs reagent, and in addition, the wavelength of its u.v. absorption maximum (λ_{max} 277 nm), agrees very well with that calculated from Scott's rule[12] for

[12] Scott, A. I., in 'Interpretation of the Ultraviolet Spectra of Natural Products' p. 109 (Pergamon Press: London 1964).

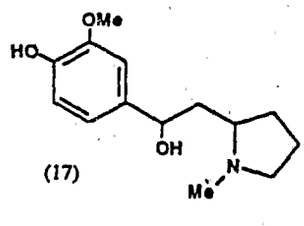
a 4-hydroxy-3-methoxy-acetophenone (λ_{max} 278 nm). This substitution pattern is also in accord with biogenetic considerations.

The mass spectrum revealed a weak molecular ion at *m/z* 249, and a base peak at *m/z* 84; the appearance of the latter ion suggested that phyllostone contained a 2-substituted *N*-methylpyrrolidine moiety, and thus it could be represented by the structure (4). A prominent ion at *m/z* 166 could be formed by a McLafferty rearrangement, and two ions at *m/z* 151 and 123 could arise from that at *m/z* 166 by loss of CH_3 followed by CO. Structure (4) is consistent with evidence from the sodium borohydride reduction of phyllostone, which afforded a mixture of the two isomeric dihydrophyllostones (17): their i.r. spectra showed no carbonyl absorption band, and a molecular ion at *m/z* 251 was observed in their mass spectra.

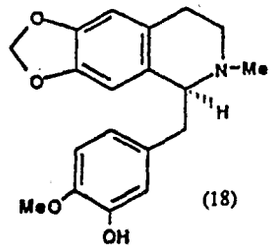
Phyllostone bears an interesting biogenetic relationship to the secophenanthroindolizidine and phenanthroindolizidine alkaloids found in the same plant *Cryptocarya phyllostemon*; phyllostone may be a key intermediate in the biosynthesis of these alkaloids, since it has been postulated that pyrrolidinylacetophenones are condensed with arylpyruvic acids *in vivo* to form septicine-type alkaloids, which after cyclization afford antofine-type alkaloids.[7,9] Phyllostone is the first example of a pyrrolidine alkaloid bearing a 2-arylacetyl group, but two analogues with a piperidine ring are known; one of them, pleurospermine, was isolated from another species of *Cryptocarya*, *C. pleurosperma*, where it co-occurs with two biogenetically-related phenanthroquinolizidine alkaloids.[7]

Dibenzopyrrocolines

Three quaternary dibenzopyrrocoline alkaloids were obtained as their chloride salts from *Cryptocarya phyllostemon*. One of them was identified as (–)-cryptowoline (6), which has been isolated once only, 35 years ago, from the Australian *Cryptocarya bowiei*.[13,14] The other two are new products: they have been named cryptowolidine and cryptowolinol and their structural elucidation has been recently reported.[15] (–)-Cryptowolidine (7) is isomeric with cryptowoline (6) with a methoxyl and a hydroxy phenolic group at C2 and C3 respectively. (–)-Cryptowolinol (8) is a 12-hydroxycryptowoline in which the original feature consists in the unusual presence of an alcoholic hydroxyl on the benzylic carbon.



(17)



(18)

[13] Ewing, J., Hughes, G. K., Ritchie, E., and Taylor, W. C., *Nature (London)*, 1952, **169**, 618.
[14] Ewing, J. Hughes, G. K., Ritchie, E., and Taylor, W. C., *Aust. J. Chem.*, 1953, **6**, 78.
[15] Lebœuf, M., Cavé, A., Ranaivo, A., and Moskowitz, H., *Can. J. Chem.*, 1989, **67**, 947.

Benzyltetrahydroisoquinoline Alkaloids.

Two new quaternary benzyltetrahydroisoquinoline alkaloids, for which the names phyllocryptine and phyllocryptonine are proposed, were isolated as chlorides from stem bark of *Cryptocarya phyllostemon*.

(+)-Phyllocryptine (9) has the molecular formula $C_{20}H_{24}N^+O_4$ and a u.v. spectrum consistent with a benzyltetrahydroisoquinoline; its phenolic nature was deduced from the bathochromic shift observed in alkaline medium. The chemical ionization mass spectrum shows, in addition to the molecular ion at *m/z* 342, a strong peak at *m/z* 341 and a base peak at *m/z* 327; the latter can be interpreted as due to loss of one of the *N*-methyls attached to the quaternary nitrogen. An electron impact mass spectrum provides additional information: the base peak at *m/z* 58 corresponds to a retro Diels–Alder elimination of the fragment $H_2C{=}N^+Me_2$ following the opening of ring B of a quaternary benzyltetrahydroisoquinoline. Another prominent fragment at *m/z* 190, resulting from the rupture of the benzylic link between C1 and Cα after elimination of one of the *N*-methyl groups, indicates that ring A is substituted by a methylenedioxy group; finally, a weak peak at *m/z* 137 shows that the benzylic ring bears a methoxyl and a phenolic hydroxy group.

The ^{1}H n.m.r. spectrum is in accord with these deductions, and confirms that phyllocryptine is an *N,N*-dimethylbenzyltetrahydroisoquinoline substituted at positions 6 and 7 by a methylenedioxy group; carbons 3′ and 4′ must bear a hydroxyl and a methoxyl, although the spectroscopic data available do not allow the respective positions to be defined. However, structure (9) in which the hydroxyl is at C3′ and the methoxyl at C4′ is assigned to phyllocryptine from the fact that the alkaloid gives a positive Gibbs reaction, indicating the presence of a phenolic group unsubstituted in the *para* position; this substitution pattern, moreover, is supported by biogenetic considerations: in the same plant the alkaloid phyllocryptonine (10) is present, in which the substitution of the benzylic ring by a hydroxyl at C3′ and a methoxyl at C4′ has been established in an unequivocal manner (see below); moreover, this type of substitution is biogenetically 'normal', since it has been shown that in laudanosoline the hydroxyl at C4′ is methylated before that at C3′.[16]

The dequaternization of phyllocryptine (9) was carried out by refluxing it with sodium thiophenate in butan-2-one under nitrogen;[17] under these conditions, a tertiary amine was obtained, whose spectroscopic data are in accord with the expected structure (18). This alkaloid, which does not seem to have been recorded previously, has been named *N*-demethylphyllocryptine. Finally, the configuration 1-*S* has been deduced for phyllocryptine from the positive sign of its optical rotation, and confirmed by observation of its c.d. spectrum, which shows two positive Cotton effects at 243 and 290 nm.[18]

It seems probable that phyllocryptine arises *in vivo* from reticuline by two classical reactions in plant biochemistry: quaternization of the nitrogen and formation of a methylenedioxy group from an *ortho*-methoxyphenol. However,

[16] Zenk, M. H., in 'The Chemistry and Biology of Isoquinoline Alkaloids' (Eds J. P. Phillipson, M. F. Roberts, and M. H. Zenk) p. 240 (Springer-Verlag: Berlin–Heidelberg 1985).
[17] Shamma, M., Deno, N. C., and Remar, J. F., *Tetrahedron Lett.*, 1966, 1375.
[18] Shamma, M., and Moniot, J. L., in 'Isoquinoline Alkaloids Research 1972–1977' (Plenum Press: New York 1978).

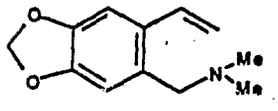
it must be pointed out that reticuline itself has not been isolated from *Cryptocarya phyllostemon*, and also that the presence of a methylenedioxy group is rare in the benzyltetrahydroisoquinoline series in contrast to other natural isoquinoline nuclei, in particular the aporphines.

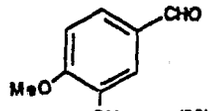
(+)-Phyllocryptonine constitutes the major component amonst the quaternary alkaloids isolated from *Cryptocarya phyllostemon*. Its ^{1}H n.m.r. spectrum shows many analogies with that of phyllocryptine (9), but it has in addition two one-proton doublets at δ 5·18 and 4·66 (J 6 Hz), which can be attributed respectively to one proton on a carbon bearing an alcoholic hydroxyl, and another on a trisubstituted carbon vicinal to the latter carbon. Acetylation of phyllocryptonine leads to an *O,O*-diacetyl derivative whose ^{1}H n.m.r. spectrum shows the presence of two acetyl groups, one phenolic and one alcoholic, at δ 2·26 and 2·16, and also of the two doublets previously mentioned which are now deshielded by the acetylation and appear at δ 6·35 and 5·33 respectively.

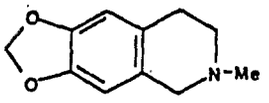
The c.i. mass spectrum of phyllocryptonine indicates a molecular mass of 358, *i.e.* 16 mass units more than phyllocryptine (9), corresponding to the formula $C_{20}H_{24}N^+O_5$. The electron impact mass spectrum reveals several interesting fragments: a peak at *m/z* 341 arises from opening of ring B and loss of the alcoholic hydroxyl; subsequent elimination of the ion $H_2C{=}N^+Me_2$ leads to the well-known fragment *m/z* 58. In addition, four peaks at *m/z* 343, 190, 153 and 152 are observed, the first of which corresponds to the loss of one of the methyls attached to the quaternary nitrogen; the tertiary amine then undergoes the usual benzylic fragmentation of benzyltetrahydroisoquinolines to give on the one hand the ion at *m/z* 190 corresponding to the isoquinoline part of the molecule bearing the methylenedioxy group, and on the other hand to the fragments *m/z* 153 and 152; the latter arises from the benzylic nucleus bearing a methoxyl, a phenolic hydroxyl, and a CHO group resulting from oxidation of the benzylic carbon Cα. The existence of this fragment supports the presence in phyllocryptonine of an alcoholic hydroxyl attached to Cα, in accord with the ^{1}H n.m.r. data.

Attempted *O*-methylation of phyllocryptonine with diazomethane results in cleavage of the molecule at the benzylic bond and the opening of ring B between the nitrogen and C3, instead of the expected methylation of the phenolic hydroxyl. Two products were thus isolated and identified, the first as the vinyl benzylamine (19) (49% yield), and the second as 3-hydroxy-4-methoxybenzaldehyde (20) (isovanillin). Elimination reactions of the Hofmann type produced by diazomethane similar to that occurring here have been previously observed with other quaternary isoquinolines.[19,20] When submitted to a Hofmann reaction under standard conditions, phyllocryptonine likewise undergoes opening of ring B and rupture of the benzylic link; in the same way, pyrolysis under vacuum of phyllocryptonine hydroxide leads to the same products (19) and (20). The isolation of the latter enables the phenolic hydroxy group to be fixed with certainty at C3′ and the methoxyl at C4′, and in consequence the plane structure indicated by (10) can be attributed to phyllocryptonine, which is also in accord with the ^{13}C n.m.r. data.

[19] Naghaway, J. A., Shaath, N., and Soine, T. O., *J. Org. Chem.*, 1975, **40**, 539.
[20] Naghaway, J. A., and Soine, T. O., *J. Pharm. Sci.*, 1978, **67**, 473.


(19)


(20)


(21)

An attempt was made to dequaternize phyllocryptonine (10) by the same method as that used for phyllocryptine (9). The action of sodium thiophenate on (10) produced in fact dequaternization, but it was accompanied by rupture of the benzylic linkage, and the product obtained has been identified as hydrohydrastinine (21).[21]

The plane structure of phyllocryptonine (10) having been established, it remained to determine the absolute configuration. The stereochemistry at C1 can be deduced as 1-*S*, from the fact that the c.d. spectrum shows a negative Cotton effect at 240 nm. The configuration at Cα is more difficult to fix: the values observed in the n.m.r. spectrum of phyllocryptonine for the chemical shifts of the protons on C1 and Cα on the one hand, and for their coupling constants on the other, do not allow the relative configurations at these centres to be determined in the light of previous observations in the case of synthetic α-hydroxylated benzyltetrahydroisoquinolines.[22,23] This problem could only be resolved by the synthesis of the *erythro* and *threo* isomers of phyllocryptonine, and comparison with the natural product. This synthesis (see below) has shown that the natural phyllocryptonine is the *threo* derivative, and its absolute configuration is thus 1-*S*,α-*S*. The configuration of phyllocryptonine (10) is the inverse of that of phyllocryptine (9), a rather surprising fact in view of their presence in the same plant. However, it should be noted in this connection that the stage at which the hydroxyl is introduced at Cα is unknown, and that if phyllocryptonine were to be formed from phyllocryptine through an enamine intermediate, it would be quite possible to have inverse configurations at C1 for these two alkaloids.

Attention should be drawn to the presence of cryptowolinol (8) and phyllocryptonine (10) together in *Cryptocarya phyllostemon*. These two quaternary bases have in common the same novel feature, an alcoholic hydroxyl attached to the benzylic carbon, C12 or Cα. It is considered that from a biogenetic point of view the dibenzopyrrocoline skeleton has a benzyltetrahydroisoquinoline as a precursor,[24] and it is thus possible that an analogue of phyllocryptonine could lead *in vivo* to cryptowolinol.

Synthesis of Phyllocryptonine

For this synthesis we have followed a sequence (Scheme 1) suggested by the work of Kametani *et al.*:[22] condensation of 3,4-methylenedioxy-β-phenylethylamine (22) with the acid chloride of 3-benzyloxy-4-methoxyphenylacetic acid (23) giving 2-(3-benzyloxy-4-methoxyphenyl)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]acetamide (24). The amine (22) was itself

[21] Menachery, M. D., Lavanier, G. L., Wetherley, M. L., Guinaudeau, H., and Shamma, M., *J. Nat. Prod.*, 1986, **49**, 745.
[22] Kametani, T., Matsumoto, H., Satoh, Y., Nemoto, H., and Fukumoto, K., *J. Chem. Soc. Perkin Trans. 1*, 1977, 376.
[23] Kessar, S. V., Mohammad, T., and Gupta, Y. P., *Indian J. Chem.*, 1983, **22B**, 321.
[24] Elliott, I., in 'The Alkaloids' (Ed. A. Brossi) Vol. 31, p. 101 (Academic Press: New York 1987).

obtained by reduction of the corresponding nitrile (commercially available or prepared from piperonal, reduced to the alcohol, then transformed into the chloro derivative and subsequently the nitrile); the acid chloride (23) was prepared by standard methods[25–27] starting from benzylisovanillin.

2-(3-Benzyloxy-4-methoxyphenyl)-*N*-[2-(3,4-methylenedioxyphenyl)ethyl]-acetamide (24) was cyclized to 1-(3-benzyloxy-4-methoxybenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (25) by the action of phosphorus oxychloride in benzene.[28] On shaking with air, the dihydroisoquinoline (25) was oxidized[22] to a keto imine (26) which was methylated to an immonium salt (27). The reduction of (27) by sodium borohydride led to *N*-methyl-1,2,3,4-tetrahydroisoquinoline (28). A single product was isolated, which is the racemic *threo* or *erythro* compound characterized by an ^{1}H n.m.r. signal at δ 3·61 (d, J 4·5 Hz, H1) and by another at δ 4·85 (d, J 4·5 Hz, Hα). According to Kametani *et al.*[22] and Kessar *et al.*,[23] in structures of this type the coupling constants between protons attached to C1 and Cα are smaller for the *erythro* ($J \approx 5$ Hz) than for the *threo* isomer ($J \approx 8$ Hz). In the case of (28), the observed value thus indicates an *erythro* configuration (1-*R,S*; α-*S,R*).

The debenzylation of (28) led to a mixture of two products (29) and (30) (5:1, respectively), separable by column chromatography. The structures of these compounds were determined by analysis of their spectra: on the one hand, the u.v. spectra were identical, and the mass spectra showed the same characteristic fragmentations; on the other hand, the ^{1}H n.m.r. spectra (Table 1) revealed distinct differences. A comparison of these results with those quoted above[22,23] permits the following deductions to be made, and allows the relative configurations of the two products (29) and (30) to be established.

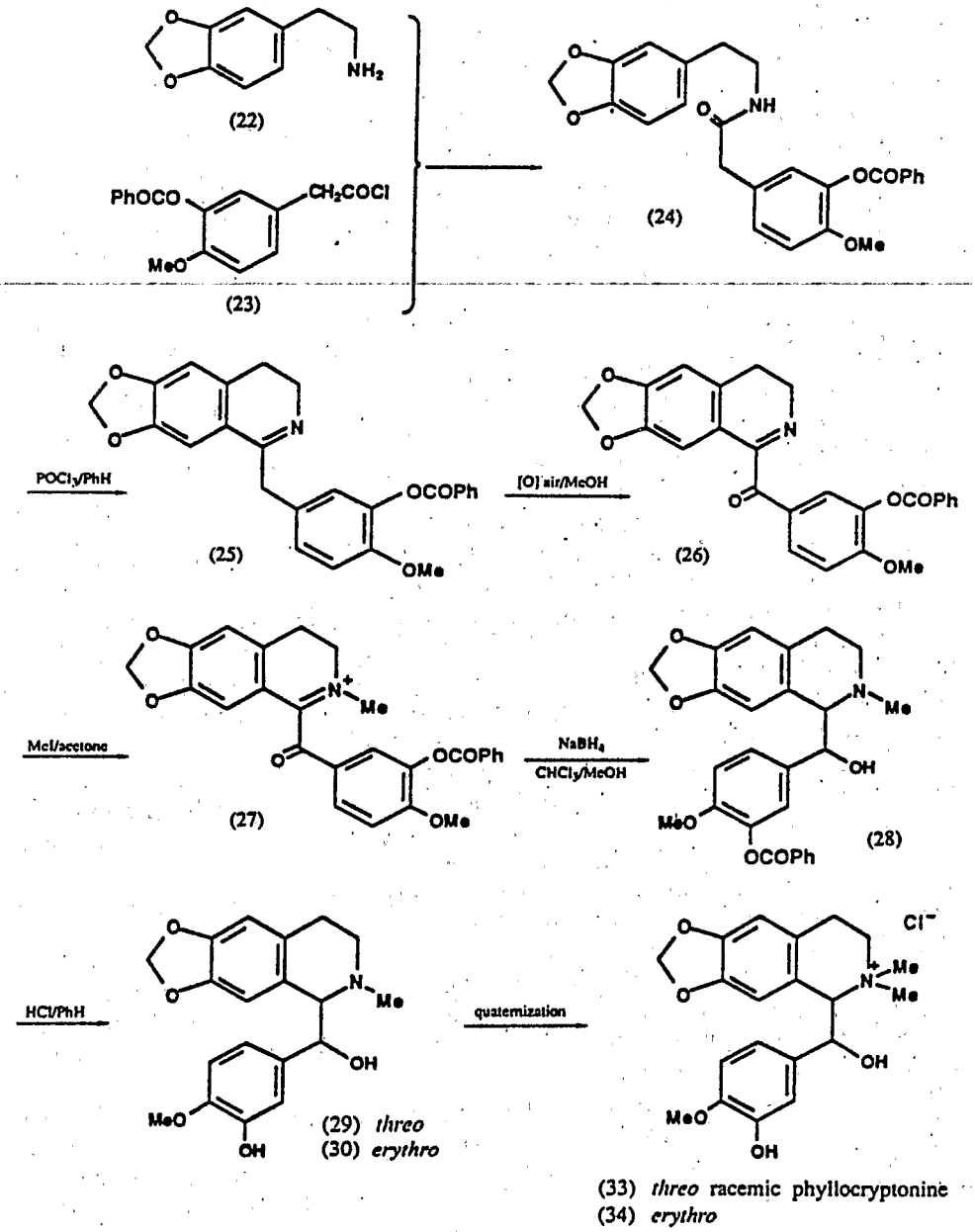
The main product (29), which has the higher $J_{H1,H\alpha}$ coupling constant (J 9 Hz), must be the *threo* isomer, and the minor one (30) with the lower $J_{H1,H\alpha}$ value (J 5 Hz) must be the *erythro* isomer. Before debenzylation, (28) was the *erythro* isomer, and the liberation of the phenolic group could not have altered its stereochemistry. After the reaction, two isomers were obtained, the *threo* isomer predominating. The following hypothesis can be proposed to explain this behaviour: in acid medium, the alcohol (28) forms a carbonium ion which, on attack by a molecule of water, affords pairs of *erythro* and *threo* isomers; the latter pair, being thermodynamically more stable, is the major product, resulting in the equilibrium shown in Scheme 2.

In order to verify this hypothesis we debenzylated the keto imine (26), the derivative (31) thus obtained was methylated, and the corresponding immonium salt (32) was reduced (Scheme 3). Under these conditions, only one product was isolated, and the spectroscopic evidence indicated that it was the *erythro* isomer (30).

The tertiary bases (29) and (30) reacted readily with methyl iodide in acetone solution to give the corresponding quaternary ammonium iodides. These iodides were either transformed directly into chlorides by passing through an ion exchange resin (IRA 400), or taken up in dilute hydrochloric acid, then

[25] Robinson, R., and Sugasawa, S., *J. Chem. Soc.*, 1931, 3163.
[26] Friedman, L., and Schechter, H., *J. Org. Chem.*, 1960, **25**, 877.
[27] Naik, R. G., and Wheeler, T. S., *J. Chem. Soc.*, 1938, 1780.
[28] Kametani, T., and Fukumoto, K., *J. Chem. Soc. C*, 1971, 2709.

precipitated in the form of iodomercurates with concentrated Mayer's reagent before passage through the resin. The same products were obtained in the two cases, the second method serving for purification. The *threo* (33) and *erythro* (34) isomers of racemic phyllocryptonine chloride were thus isolated, derived respectively from the *threo* (29) and *erythro* (30) tertiary amines.



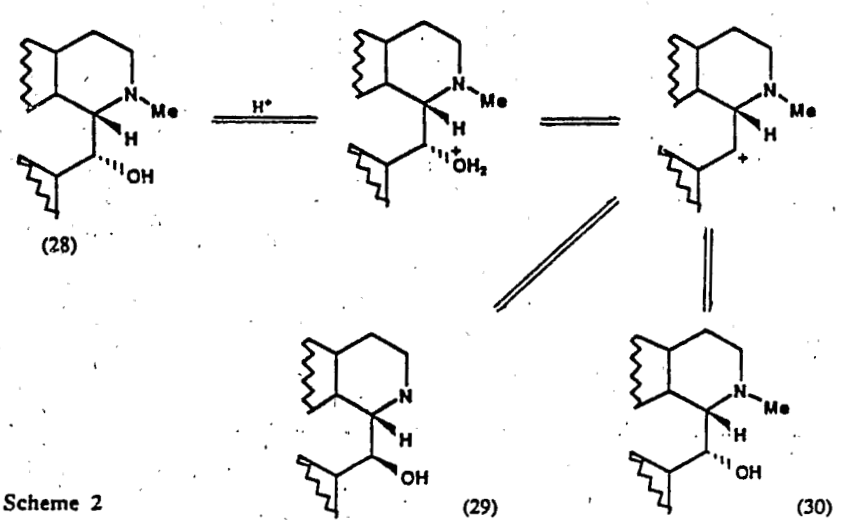
Scheme 1. Synthesis of the quaternary tetrahydrobenzylisoquinolines *threo* (33) and *erythro* (34).

The chloride of the *threo* isomer (33) crystallized from diethyl ether. Its melting point (189°C) differed from that of natural chiral phyllocryptonine chloride (10) (230°C), but the structural identity of the natural and synthetic products was established from spectroscopic data; in particular, the ^{1}H n.m.r. spectra of the two products were identical (Table 2). This identity allows the configuration 1-*S*,α-*S* to be assigned to natural phyllocryptonine (10).

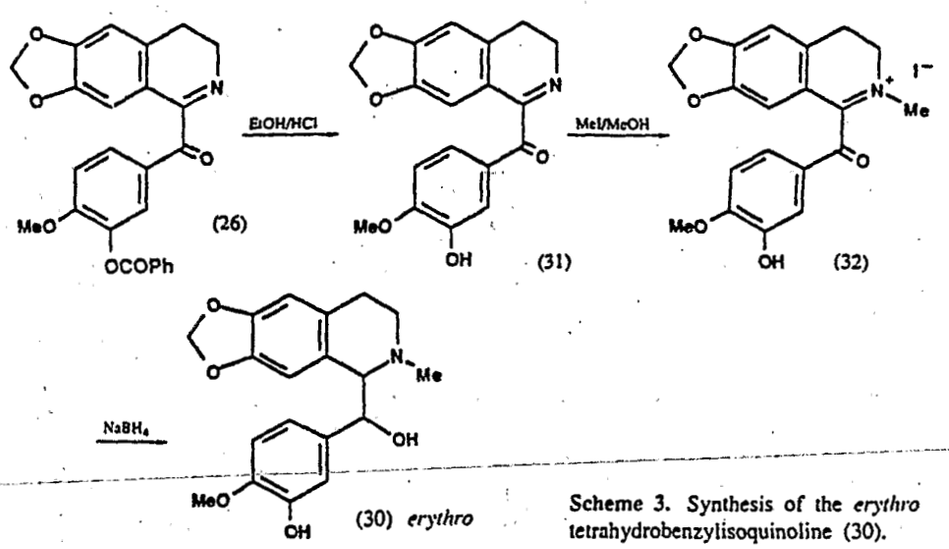
The chloride of the *erythro* isomer (34) was not obtained crystalline. Its R_F value on t.l.c. was identical with that of (33) and the mass spectra and u.v. spectra of the two samples were likewise identical, but an examination of the ^{1}H n.m.r. spectra (Table 2) showed that the two quaternary compounds are different. The n.m.r. differences are essentially associated with the chemical shifts of the protons on C8, C1 and Cα; in addition, the coupling constant between the latter two protons is 2 Hz for (34), instead of 6 Hz for (33). The quaternary compound (34) formed from the tertiary *erythro* amine (30) has the same relative *erythro* configuration, in accord with the observed weak coupling constant $J_{H1,H\alpha}$. It may be noted that on quaternization of the tertiary amines (29) and (30), the variation in the value of the coupling constant is affected in

Table 1. ^{1}H n.m.r. data of *threo* (29) and *erythro* (30) isomers in $CDCl_3$ at 60 MHz

Compound (29)	Compound (30)	Assignment
2·51 (s)	2·50 (s)	NMe
3·38 (d, *J* 9 Hz)	3·68 (d, *J* 5 Hz)	H1
3·88 (s)	3·78 (s)	4′-OMe
4·30 (d, *J* 9 Hz)	4·90 (d, *J* 5 Hz)	Hα
5·55 (s)	6·00 (s)	H8
5·81 (dd, *J* 2 Hz)	5·78 (s)	6,7-OCH_2O
6·55 (s)	7·46 (s)	H5
6·63 (d, J_o 9 Hz)		H5′
6·83 (dd, J_o 9, J_m 2 Hz)	6·60–6·78 (m)	H6′
6·93 (d, J_m 2 Hz)		H2′



Scheme 2



(26) (31) (32) (30) *erythro*

Scheme 3. Synthesis of the *erythro* tetrahydrobenzylisoquinoline (30).

Table 2. ^{1}H n.m.r. data of natural phyllocryptonine (10) and its racemic isomers *threo* (33) and *erythro* (34) in CD_3OD at 60 MHz

Compound (10)	Compound (33)	Compound (34)	Assignment
3·10 and 3·50 (s)	3·08 and 3·48 (s)	3·13 and 3·60 (s)	$N^+(Me)_2$
3·81 (s)	3·81 (s)	3·90 (s)	4′-OMe
4·66 (d, *J* 6 Hz)	4·65 (d, *J* 6 Hz)	4·56 (d, *J* 2 Hz)	H 1
5·18 (d, *J* 6 Hz)	5·16 (d, *J* 6 Hz)	5·60 (d, *J* 2 Hz)	H α
5·85 (s)	5·85 (s)	5·91 (s)	6,7-OCH_2O
6·23 (s)	6·21 (s)	5·40 (s)	H 8
6·68 (s)	6·65 (s)	6·75 (s)	H 5
6·57–6·90 (m)	6·55–6·91 (m)	6·72–7·10 (m)	H 2′,5′,6′

the same way: for the *threo* isomer [(29) → (33)] it is reduced from 9 to 6 Hz; this same diminution of 3 Hz is observed for the *erythro* isomer [(30) → (34)], the value of 5 being reduced to 2 Hz.

Experimental

General

Proton magnetic resonance (^{1}H n.m.r.) spectra, unless otherwise specified, were recorded in C^2HCl_3 by using tetramethylsilane as internal standard, at 60 MHz (Varian T 60 spectrometer), or 90 MHz (Varian EM 90), or 100 MHz (Jeol JNM-4H); chemical shifts are given in δ values, coupling constants in Hz. ^{13}C n.m.r. spectra were run at 25·2 MHz with a Varian CFT 20 spectrometer. I.r. spectra, unless otherwise specified, were recorded in $CHCl_3$ on a Beckman IR-33 or a Perkin–Elmer 257 spectrophotometer. Mass spectra were run on a VG Micromass 70 spectrometer operating at 70 eV. U.v. spectra were recorded in MeOH solution with a Perkin–Elmer 124 or a Unicam SP 1800 spectrophotometer, and c.d. spectra in MeOH with a Auto-Dichrograph Mark V.

Melting points were determined on a Yanagimoto Seisakusho or a Tottoli apparatus and are uncorrected. Specific optical rotations were measured on a Bellingham–Stanley or a Schmidt–Haensch polarimeter, for the sodium D line.

Thin-layer chromatography (t.l.c.) and preparative thin-layer chromatography (p.t.l.c.) were carried out on Merck Kieselgel 60 F254. Four drops of ammonia solution were added per

100 ml of developing solvent ($CHCl_3$ or CH_2Cl_2 containing variable amounts of MeOH), except for those solvent systems consisting of $CHCl_3/Et_2NH$ or $CHCl_3/Et_3N$.

Plant Material

Two samples of *Cryptocarya phyllostemon* were independently studied. The first plant material, consisting of leaves, twigs, roots and fruit, was collected in April 1974 from a small tree growing on peridotitic soil in the Haute Ouinné valley (New Caledonia), at a height of 750 m; a voucher specimen (Sévenet 644) has been lodged at the Muséum National d'Histoire Naturelle in Paris. The second sample, consisting of stem bark, was collected in a nearby location in November 1977, and a specimen (PC NC 219) has been deposited at the ORSTOM herbarium in Noumea.

Alkaloids of *Cryptocarya phyllostemon* Kostermans

Extraction Procedure

Different procedures were used to extract the two samples of plant material.

First sample. The ground plant material (1·85 kg) was extracted with methanol in a Soxhlet apparatus, and the extract was evaporated to dryness under vacuum. The residue was treated with acetic acid (1%) and the solution basified with ammonia, then exhaustively extracted with chloroform; the aqueous solution was reserved for recovery of quaternary alkaloids. The chloroform solution was evaporated under vacuum, the residue extracted with sulfuric acid, then the solution was basified and again extracted with chloroform. T.l.c. showed the presence of six bases in the extract, which was concentrated and subjected to distribution between chloroform (stationary phase) and aqueous sulfuric acid (10^{-3} N) in a Craig machine (100×40-ml tubes). The partially separated material emerging was grouped into fractions which were further purified by p.t.l.c.; chloroform containing variable amounts of methanol (8–15%, v/v) or triethylamine (5–10%, v/v) was used for development. The following alkaloids were obtained successively: phyllosteminine (3) (47 mg), antofine (1) (1·53 g), phyllostemine (2) (133 mg) and phyllostone (4) (74 mg). The phyllostemine from one of the fractions was contaminated with an impurity that was eventually removed by h.p.l.c. on a glass column packed with Merck silica gel 60 and eluted with $MeOH/CHCl_3$ (2:3, v/v).

The crude quaternary alkaloids from the extraction, together with further amounts contained in the basified aqueous solution from the Craig machine, were precipitated as reineckate. The complex was converted into chloride (5·2 g) by the procedure of Schmid *et al.*,[29] and a portion of the crude chloride mixture (2 g) was purified by d.c.c.c. in 100 tubes (1 m×4 mm diameter) apparatus. As solvent, a mixture of $CHCl_3/MeOH/H_2O$ (35:65:40, v/v) was used, which formed two phases; the lower one was kept stationary and the upper one used as moving phase. The two products obtained, of which one corresponded to phyllocryptine (9) (44 mg) and the other to phyllocryptonine (10) (62 mg), were still contaminated with impurity. Another portion of crude chloride mixture was stirred with sodium perchlorate in hot methanolic solution for 30 min. The precipitate after recrystallization from methanol afforded yellow crystals of dehydroantofine perchlorate; this was converted into the chloride (5) on a column of Amberlite IR 45 (Cl^-).

Second sample. The ground stem bark (600 g) was first defatted by extraction with petroleum ether in a Soxhlet apparatus, then the dried material was exhaustively extracted with 80% ethanol at room temperature in a percolator until it gave a negative Mayer reaction. The concentrated extract was taken up in 2% aqueous citric acid, then twice extracted with diethyl ether, the evaporation of which left a non-alkaloidal residue. The aqueous phase was then basified with ammonia and extracted with chloroform; the organic phase, after being washed with water, dried over anhydrous sodium sulfate and evaporated to dryness, gave a residue (0·84 g, 0·14% yield) of non-quaternary alkaloids. T.l.c. analysis showed the presence of one base only, which was recrystallized from methanol to give 570 mg of pure antofine (1).

The above-mentioned aqueous phase, which still gave a positive Mayer test, was acidified to pH 1 with concentrated hydrochloric acid, and the quaternary bases were precipitated by addition of concentrated Mayer reagent to give 84 g of iodomercurates, representing a 4·5%

[29] Kahn, Z. M., Hesse, M., and Schmid, H., *Helv. Chim. Acta*, 1965, **48**, 1957.

content of quaternary alkaloids. A portion (12 g) of the precipitate was dissolved in a mixture of $Me_2CO/MeOH/H_2O$ (6:2:1, v/v) and transformed into chlorides by passage through a column of Amberlite IRA 400 (Cl^-); 5·1 g of mixed chlorides were thus obtained which were dissolved in a mixture of $CHCl_3/MeOH/NH_4OH$ (70:30:8, v/v) and chromatographed on a column of Kieselgel 60 H (Merck, Art. 7736) with the same solvent system. The following alkaloids were isolated successively and purified by crystallization or by p.t.l.c.: cryptowolidine (7) (90 mg), cryptowoline (6) (320 mg), cryptowolinol (8) (810 mg), phyllocryptine (9) (190 mg), and phyllocryptonine (10) (1·69 g).

Characterization, Identification and Structure Determination of Individual Alkaloids

Antofine (1) and phyllostemine (2).—Antofine (1) was obtained as pale yellow needles after recrystallization from Me_2CO or MeOH, m.p. 213°, $[\alpha]_D$ −164° (*c*, 0·98 in $CHCl_3$) [lit.[30] m.p. 212–214°, $[\alpha]_D$ −165° ($CHCl_3$)]. The spectroscopic data were in complete accord with those of an authentic sample of antofine.

Phyllostemine (2) was obtained as pale yellow crystals, m.p. 200–202° (dec.) from $MeOH/CHCl_3$, or m.p. 205–207° (dec.) from pyridine, $[\alpha]_D$ −8° (*c*, 0·28 in EtOH). U.v. λ_{max} (log ϵ) 233sh (3·63), 287 nm (3·45); after addition of 1 drop of 5% aqueous NaOH, λ_{max} 247sh, 297 nm. I.r. (Nujol) ν_{max} 3560, 3340, 3200, 1610, 1590, 1510, 1460, 1290, 1260, 1200, 1160, 1030, 860, 830 cm^{-1}. ^1H n.m.r. δ ($C^2HCl_3+C^2H_3O^2H$ at 270 MHz) 3·06, d, *J* 16 Hz, 1H, H 8; 3·54, s, 3H, 3′-OMe; 3·82, d, *J* 16 Hz, 1H, H 8; 6·44, d, *J* 2 Hz, 1H, H 2′; 6·59, dd, *J* 9, *J′* 2 Hz, 1H, H 6′; 6·62, d, *J* 9 Hz, 2H, H 3″,5″; 6·68, d, *J* 9 Hz, 1H, H 5′; 6·87, d, *J* 9 Hz, 2H, H 2″,6″. M.s. *m/z* 337 (M, 98%) (Found: 337·1674. $C_{21}H_{23}NO_3$ requires 337·1678), 336 (22), 269 (21), 268 (100) (Found: 268·1098. $C_{17}H_{16}O_3$ requires 268·1099), 267 (10), 253 (14), 252 (5), 251 (12), 244 (17), 238 (7), 237 (22), 236 (12), 235 (12), 219 (7), 214 (10), 212 (7), 208 (7), 207 (7), 161 (7), 137 (17), 131 (5), 115 (5), 113 (5), 111 (7), 107 (9), 99 (9), 98 (7), 97 (14), 85 (16), 84 (9), 83 (14), 71 (24), 70 (71), 69 (17).

O-Methylation of phyllostemine (2).—A small sample of phyllostemine (15 mg) in MeOH was treated with an excess of an ethereal solution of diazomethane. After being allowed to stand overnight, the solvents were removed in vacuum, leaving a residue which was subjected to p.t.l.c., 3% $MeOH/CHCl_3+NH_3$ being used as solvent. *O,O-Dimethylphyllostemine* (11) was obtained as a yellow-green oily product (9 mg). I.r. ν_{max} 2840, 2780, 1610, 1580, 1515, 1470, 1440, 1415, 1380, 1290, 1250, 1170, 1140, 1100, 1030, 830, 805 cm^{-1}. ^1H n.m.r. δ 3·58, s, 3H, 3′-OMe; 3·75, s, 3H, 4′- or 4″-OMe; 3·83, s, 3H, 4″- or 4′-OMe; 6·48, d, *J* 2 Hz, 1H, H 2′; 6·69, m, 2H, H 5′,6′; 6·70, d, *J* 9 Hz, 2H, H 3″ and H 5″; 6·99, d, *J* 9 Hz, 2H, H 2″,6″. M.s. *m/z* 365 (M, 49%), 364 (11), 359 (6), 350 (6), 297 (15), 296 (70), 295 (6), 281 (10), 266 (21), 265 (100), 264 (5), 250 (5), 234 (12), 151 (12), 121 (8), 69 (5).

Phyllosteminine (3).—Phyllosteminine (3) was obtained as colourless *crystals*, m.p. 207–209° (dec.) from $CHCl_3$, $[\alpha]_D$ −49° (*c*, 0·4 in EtOH). U.v. λ_{max} (log ϵ) 238sh (3·93), 288 nm (3·80); after addition of 1 drop of 5% aqueous NaOH, λ_{max} 245, 290. I.r. (Nujol) ν_{max} 3200, 1600, 1570, 1510, 1470, 1290, 1240, 1160, 1090, 1030, 960, 920, 820, 800, 750 cm^{-1}. ^1H n.m.r. δ (C^2HCl_3 at 270 MHz) 3·25, d, *J* 17 Hz, 1H, H 8; 3·97, d, *J* 17 Hz, 1H, H 8; 4·47, d, *J* 8 Hz, 1H, H 5; 5·85, s, 2H, 3′,4′-OCH_2O; 6·49, dd, *J* 8, *J′* 2 Hz, 1H, H 6′; 6·52, d, *J* 2 Hz, 1H, H 2′; 6·59, d, *J* 8 Hz, 2H, H 3″,5″; 6·62, d, *J* 8 Hz, 1H, H 5′; 6·79, d, *J* 8 Hz, 2H, H 2″,6″. M.s. (c.i.) *m/z* 352·1549 (M+1) ($C_{21}H_{22}NO_4$ requires 352·1526), 334·1433 [(M+1)−18] ($C_{21}H_{20}NO_3$ requires 334·1441). M.s. (e.i.) *m/z* 351 (M, 4%), 298 (9), 283 (9), 282 (70), 281 (8), 254 (9), 253 (8), 252 (7), 251 (6), 238 (6), 224 (5), 223 (7), 195 (7), 160 (16), 159 (5), 121 (15), 120 (5), 70 (8), 69 (100).

O-Methylation of phyllosteminine (3).—Phyllosteminine (15 mg) was treated with diazomethane as indicated above for the *O*-methylation of phyllostemine (2); *4″-O-methylphyllosteminine* (13) was obtained as a colourless gum (12 mg). I.r. ν_{max} 3360, 2820, 2800, 2790 (Bohlmann bands), 1600, 1505, 1480, 1455, 1430, 1280, 1170, 1090, 1030, 960, 930, 820, 800 cm^{-1}. ^1H n.m.r. δ 3·76, s, 1H, 4″-OMe; 4·48, br s, 1H, H 5; 5·92, s, 2H, 3′,4′-OCH_2O; 6·60, br s, 1H, H 2′; 6·70, d, *J* 9 Hz, 4H, H 5′,6′,3″,5″; 6·95, d, *J* 9 Hz, 2H, H 2″,6″. M.s. *m/z* 365 (M, 10%), 346 (6), 343 (21), 313 (7), 312 (29), 297 (24), 296 (100), 295

[30] Wiegrebe, W., Faber, L., Brockmann, H., Budzikiewicz, H., and Krüger, U., *Justus Liebigs Ann. Chem.*, 1969, 721, 154.

(12), 282 (6), 281 (22), 268 (10), 267 (10), 266 (9), 265 (12), 253 (7), 252 (6), 238 (6), 237 (12), 223 (6), 174 (19), 135 (12), 120 (9), 84 (37), 83 (9), 82 (56), 70 (13), 69 (100), 68 (12).

Acetylation of 4″-O-methylphyllosteminine (13).—4″-*O*-Methylphyllosteminine (12 mg) in anhydrous pyridine (6 ml) was treated with acetic anhydride (1 ml) at room temperature for 36 h. The solvent was evaporated, and the residue was diluted with water and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to dryness under vacuum. The product was subjected to p.t.l.c., 5% MeOH/$CHCl_3$+NH_3 being used as solvent, and afforded the *5-O-acetyl derivative* (14) as an oily yellow material (5 mg). I.r. ν_{max} 2800, 2700, 1730, 1600, 1570, 1510, 1480, 1435, 1360, 1320, 1280, 1170, 1100, 1030, 950, 930, 820, 800 cm^{-1}. ^1H n.m.r. δ (C^2HCl_3 at 270 MHz) 1·77, s, 3H, 5-OAc; 3·74, s, 3H, 4″-OMe; 5·86, s, 2H, 3′,4′-OCH_2O; 6·48, d, *J* 2 Hz, 1H, H 2′; 6·49, dd, *J* 8 Hz, *J′* 2 Hz, 1H, H 6′; 6·59, d, *J* 8 Hz, 1H, H 5′; 6·69, d, *J* 8 Hz, 2H, H 3″,5″; 6·95, d, *J* 8 Hz, 2H, H 2″,6″. M.s. *m/z* 407 (M, 7%), 348 (15), 347 (27), 346 (35), 339 (12), 338 (50), 319 (5), 297 (22), 296 (100), 295 (12), 281 (8), 279 (7), 278 (17), 268 (5), 267 (5), 266 (5), 265 (10), 237 (7), 209 (5), 121 (8), 70 (5).

Phyllostone (4).—Phyllostone (4) was obtained as a colourless *gum*, $[\alpha]_D$ −5° (*c*, 0·69 in EtOH). U.v. λ_{max} (log ϵ) 229 (4·01), 277 (3·87), 305 nm (3·83); after addition of 1 drop of 5% aqueous NaOH, λ_{max} 247, 346 nm. I.r. ν_{max} 3500, 1655, 1580, 1500, 1450, 1415, 1250, 1150, 1020, 870 cm^{-1}. ^1H n.m.r. δ 2·65, s, 3H, NMe; 3·84, s, 3H, 3-OMe; 6·89, d, *J* 8 Hz, 1H, H 5; 7·35, d, *J* 2 Hz, 1H, H 2; 7·40, dd, *J* 8, *J′* 2 Hz, 1H, H 6. M.s. *m/z* 249 (M, 2%) (Found: 249·1365. $C_{14}H_{19}NO_3$ requires 249·1346), 166 (15), 151 (34), 123 (11), 98 (9), 97 (6), 85 (11), 84 (100), 83 (23), 82 (23), 81 (6).

O-Methylation of phyllostone (4).—Phyllostone (15 mg) was *O*-methylated as described for compound (2). The methylated product was purified by p.t.l.c., 12% MeOH/$CHCl_3$+NH_3 being used as solvent. After multiple development, *O-methylphyllostone* (16) was obtained as a colourless oily product (11 mg). I.r. ν_{max} 1680, 1595, 1510, 1460, 1410, 1340, 1300, 1270, 1150, 1020, 870, 800 cm^{-1}. ^1H n.m.r. δ 2·51, s, 3H, NMe; 3·98, s, 6H, 3- and 4-OMe; 6·93, d, *J* 9 Hz, 1H, H 5; 7·57, d, *J* 3 Hz, 1H, H 2; 7·67, dd, *J* 9, *J′* 3 Hz, 1H, H 6. M.s. *m/z* 263 (M, 22%), 180 (33), 166 (11), 165 (100), 151 (9), 137 (14), 122 (10), 109 (5), 98 (27), 85 (37), 84 (59), 83 (75), 82 (49), 79 (19), 77 (22), 76 (5).

Reduction of phyllostone (4).—Phyllostone (15 mg) was treated with $NaBH_4$ (20 mg) in EtOH (2 ml), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the residue was diluted with water and extracted with $CHCl_3$. The solution was dried (Na_2SO_4) and evaporated to dryness under vacuum. The product (13 mg) was submitted to p.t.l.c. with 20% MeOH/$CHCl_3$+NH_3 as solvent. After multiple development, a major (8 mg) and a minor (3 mg) product were obtained. *Major reduction product* (17a): U.v. λ_{max} (log ϵ) 225 (3·75), 280 nm (3·40); after addition of 1 drop of 5% aqueous NaOH, λ_{max} 247, 290 nm. I.r. ν_{max} 3340, 1600, 1510, 1460, 1450, 1430, 1270, 1150, 1120, 1030, 1000, 850, 810 cm^{-1}. ^1H n.m.r. δ 2·65, s, 3H, NMe; 3·92, s, 3H, 3-OMe; 5·0, m, 1H, CHOH; 6·85, br s, 2H, H 5,6; 7·03, br s, 1H, H 2. M.s. *m/z* 251 (M, 17%), 151 (6), 150 (27), 135 (20), 107 (10), 99 (6), 98 (22), 97 (8), 96 (8), 85 (25), 84 (100), 83 (19), 82 (32). *Minor reduction product* (17b): U.v. λ_{max} (log ϵ) 228 (3·76), 280 nm (3·42); after addition of 1 drop of 5% aqueous NaOH, λ_{max} 248, 290 nm. I.r. ν_{max} 3400, 3150, 1590, 1510, 1450, 1420, 1265, 1140, 1115, 1050, 1025, 850, 810 cm^{-1}. ^1H n.m.r. δ 2·48, s, 3H, NMe; 3·90, s, 3H, 3-OMe; 4·80, m, 1H, CHOH; 6·81, br s, 2H, H 5,6; 6·98, br s, 1H, H 2. M.s. *m/z* 251 (M, 4%), 151 (5), 150 (33), 135 (28), 107 (15), 98 (7), 96 (6), 85 (8), 84 (100), 83 (17), 82 (30).

Dehydroantofine (5).—Dehydroantofine was isolated as its perchlorate [yellow crystals, m.p. >230° (dec.)] and shown to be identical with the product obtained from the oxidation of antofine with mercuric acetate.[30]

Reduction of dehydroantofine (5).—Dehydroantofine chloride (50 mg) was dissolved in 10% aqueous MeOH solution (10 ml) and $NaBH_4$ (300 mg) was added; then the mixture was stirred at room temperature for 45 min. The usual workup afforded a yellow solid (20 mg) which was purified by p.t.l.c. with 5% MeOH/$CHCl_3$+NH_3 as solvent. A pale yellow solid product (14 mg) was obtained, which was recrystallized from acetone, m.p. 211–213°. It was identical (^1H n.m.r., i.r., m.s., and mixed m.p.) with antofine (1).

Cryptowoline (6), cryptowolidine (7), cryptowolinol (8) and phyllocryptine (9).—Cryptowoline (6) was isolated as its chloride, m.p. 188–190° ($CHCl_3$), $[\alpha]_D$ −200° (*c*, 1·0 in EtOH). The spectroscopic data were in complete accord with those of an authentic sample of synthetic cryptowoline.

Cryptowolidine (7) and cryptowolinol (8) were also obtained as their chloride salts. Cryptowolinol chloride was amorphous, whereas cryptowolidine chloride crystallized from Me_2CO, m.p. 218–220°, $[\alpha]_D$ −152° (*c*, 1·0 in EtOH). Their spectroscopic data have been recently reported in a separate publication.[15]

Phyllocryptine (9) was isolated as its chloride, which could not be crystallized from the usual solvents; yellow amorphous powder, $[\alpha]_D$ positive (the value could not be measured because of the coloration of the solution in EtOH). U.v. λ_{max} (log ϵ) 223sh (4·38), 283 nm (4·20); after addition of 1 drop of aqueous NaOH, λ_{max} 219, 229sh, 291 nm. C.d. λ ($\Delta\epsilon$) 214·5 (+4·7), 229 (0), 243 (+1·2), 262·5 (0), 290 (+1·3), 302 (0). ^{1}H n.m.r. δ ($C^2H_3O^2H$ at 60 MHz) 3·18 and 3·45, 2s, 6H, N^+Me_2; 3·85, s, 3H, 4′-OMe; 5·88, s, 2H, 6,7-OCH_2O; 6·15, s, 1H, H8; 6·58, s, 1H, H5; 6·55–6·90, m, 3H, H2′,5′,6′. M.s. (c.i.) *m/z* 342 (M, 15%) (Found: 342·1701. $C_{20}H_{24}N^+O_4$ requires 342·1705), 341 (63), 327 (100). M.s. (e.i.) *m/z* 190 (36%), 137 (3), 58 (100).

Dequaternization of phyllocryptine (9).—To a solution of phyllocryptine (200 mg, 0·56 mmol) in EtOH (20 ml) were added 20 ml of an ethanolic solution of sodium thiophenoxide (188 mg, 1·42 mmol) prepared according to Miller *et al.*,[31] and the mixture was stirred at room temperature for 0·5 h. The ethanolic solution was filtered and evaporated to dryness under vacuum, and the residue dissolved in 80 ml of butan-2-one which had been freshly distilled over zinc. The mixture was refluxed under nitrogen for 36 h, then the solvent was evaporated. The residue was cooled and treated with 20 ml of water, and the aqueous solution was thoroughly extracted with chloroform (4×50 ml). After evaporation of the solvent, the residue was taken up in 10% hydrochloric acid. The aqueous phase was extracted with ether, then basified with aqueous sodium bicarbonate and extracted with chloroform. The chloroform solution was dried (Na_2SO_4) and evaporated under reduced pressure, leaving a residue which was chromatographed on a column of 10 g Kieselgel 60 H, with $CHCl_3$/MeOH/NH_4OH (95:5:0·2, v/v) as solvent. N-*Demethylphyllocryptine* (18) (115 mg) was thus obtained pure. (Found: C, 69·4; H, 6·4; N, 4·3. $C_{19}H_{21}NO_4$ requires C, 69·7; H, 6·5; N, 4·3%). U.v. λ_{max} (log ϵ) 222sh (4·13), 286 nm (3·59); after addition of 1 drop of aqueous NaOH, λ_{max} 230sh, 295 nm. ^{1}H n.m.r. δ 2·56, s, 3H, NMe; 3·88, s, 3H, 4′-OMe; 5·90, s, 2H, 6,7-OCH_2O; 6·23, s, 1H, H8; 6·60, s, 1H, H5; 6·70–6·80, m, 3H, H2′,5′,6′. M.s. (c.i.) *m/z* 328 (M+1, 100%), 190 (20); M.s. (e.i.) *m/z* 190 (100), 188 (9), 137 (4).

Phyllocryptonine (10).—Phyllocryptonine (10) was isolated as its chloride, obtained pure after recrystallization several times from acetone. It formed fine white *crystals*, m.p. 230–231° (Me_2CO), $[\alpha]_D$ +36° (*c*, 1·0 in EtOH). U.v. λ_{max} (log ϵ) 222sh (3·12), 290 nm (3·28); after addition of 1 drop of aqueous NaOH, λ_{max} 230sh, 300 nm. C.d. $\lambda(\Delta\epsilon)$ 214 (−6·4), 240 (−4·3), 268 (0), 295 (+2·0), 315 (0). ^{1}H n.m.r. δ ($C^2H_3O^2H$ at 60 MHz): see Table 2. ^{13}C n.m.r. δ 22·7, C4; 51·4 and 53·5, N^+Me_2; 54·3, 4′-OMe; 54·6, C3; 73·5, C1; 75·9, Cα; 100·8, 6,7-OCH_2O; 106·8, C8; 108·5, C5; 110·5, C5′; 113·3, C2′; 117·7, C6′; 121·4, C1′; 122·6, C4a; 133·8, C8a; 145·8, C7,3′; 147·0 and 147·8, C6 and C4′. M.s. (c.i.) *m/z* 358 (M, 5%) (Found: 358·1648. $C_{20}H_{24}N^+O_5$ requires 358·1654), 344 (22), 326 (1), 193 (12), 192 (100), 170 (6), 153 (23). M.s. (e.i.) *m/z* 343 (2%), 341 (2), 191 (66), 190 (100), 153 (8), 152 (65), 151 (69), 148 (55).

O-Acetylation of phyllocryptonine (10).—Phyllocryptonine (36 mg) was *O*-acetylated as indicated above for compound (13). Column chromatography of the residue on Kieselgel 60H, using $CHCl_3$-MeOH (90:10, v/v) as solvent, afforded the pure *O,O*-diacetyl derivative as a colourless *gum* (19 mg). I.r. (KBr) ν_{max} 1750 cm^{-1}. ^{1}H n.m.r. δ 2·16, s, 3H, α-OAc; 2·26, s, 3H, 3′-OAc; 3·43 and 3·70, 2s, 6H, N^+Me_2; 3·83, s, 3H, 4′-OMe; 5·33, br s, 1H, H1; 6·01, s, 2H, 6,7-OCH_2O; 6·35, br s, 1H, Hα; 6·61–7·31, m, 5H, H5,8,2′,5′,6′.

Treatment of phyllocryptonine (10) with diazomethane.—Phyllocryptonine (100 mg) was treated with CH_2N_2 as indicated above for the *O*-methylation of phyllostemine (2), and the crude reaction product was submitted to column chromatography on Kieselgel 60 H. Two compounds (19) and (20) were obtained in a pure form: the less polar product (20) (30 mg, yield 25%) was eluted with $CHCl_3$, and the more polar (19) (60 mg, yield 49%) with MeOH.

N,N-*Dimethyl-4,5-methylenedioxy-2-vinylbenzylamine* (19): colourless oil. ^{1}H n.m.r. δ 2·41, s, 6H, NMe_2; 3·68, s, 2H, CH_2NMe_2; 5·28, dd, *J* 11, *J′* 2 Hz, 1H, vinylic proton; 5·55, dd,

[31] Miller, S. I., Orzech, C. E., Welch, C. A., Ziegler, G. R., and Dickstein, J. I., *J. Am. Chem. Soc.*, 1962, 84, 2020.

J 17, *J'* 2 Hz, 1H, vinylic proton; 5·98, s, 2H, 4,5-OCH_2O; 6·91, and 7·03, 2 s, 2H, H 3,6; 7·05, dd, *J* 11, *J'* 17 Hz, 1H, $PhCH{=}CH_2$. M.s. (e.i.) *m/z* 205 (M, 69%) (Found: 205·1101. $C_{12}H_{15}NO_2$ requires 205·1103), 190 (90), 161 (89), 131 (96), 58 (88), 57 (100), 43 (68).

3-Hydroxy-4-methoxybenzaldehyde (isovanillin) (20): colourless crystals from Et_2O, m.p. 113–115°. The sample was identical (co-t.l.c., m.p., i.r., n.m.r., m.s.) with an authentic sample of isovanillin.

Hofmann reaction on phyllocryptonine (10).—Phyllocryptonine chloride (10) (100 mg) was dissolved in a 5-ml mixture of $Me_2CO/MeOH/H_2O$ (6:2:1, v/v); the solution was passed through a column of Amberlite IRA 400 (OH^-) which was eluted with the same mixture, and the residue of phyllocryptonine hydroxide obtained after evaporation of the solvent was introduced into a sublimation tube. The material was pyrolysed under vacuum at 150° for 4 h, then cooled; two products were recovered, an oil (60 mg) identical with the vinylic derivative (19), and a crystalline substance (8 mg), identical with isovanillin (20).

In another experiment phyllocryptonine chloride (10) (100 mg) was dissolved in a solution of 500 mg of potassium hydroxide in 7 ml of propan-1-ol and heated to 100° for 8 h. Water (15 ml) was added to the reaction mixture and the propan-1-ol was evaporated off. The aqueous solution was extracted with ether and the organic solution evaporated. The residue was chromatographed on a column of Kieselgel 60 H (2·5 g); elution with a mixture of $CHCl_3/MeOH/NH_4OH$ (70:30:8, v/v) led to the isolation of a pure single product (63 mg) identical with the vinylic derivative (19).

Dequaternization of phyllocryptonine (10).—Phyllocryptonine chloride (10) (100 mg) was treated with sodium thiophenoxide as indicated above for the dequaternization of phyllocryptine (9). The usual workup yielded pure *N*-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (hydrohydrastinine) (21) (19 mg), crystals from petroleum ether, m.p. 62–63°. The spectroscopic data (i.r., u.v., n.m.r., m.s.) were in complete accord with those previously reported for hydrohydrastinine.[21]

Synthesis of Phyllocryptonine

2-(3-Benzyloxy-4-methoxyphenyl)-N-[2-(3,4-methylenedioxyphenyl)ethyl]acetamide (24)

The freshly prepared chloride (23) (3·65 g) in 21 ml of benzene was added slowly to a stirred mixture consisting of 4·9 g (21 mmol) of the amine (22), 21 ml benzene, and 28 ml N sodium hydroxide solution. Stirring was continued for 3 h, during which time a white precipitate gradually formed, was filtered off, washed in turn with dilute hydrochloric acid and water, and dried. The pure amide (24) (3·7 g, yield 68%) was obtained after recrystallization from ethanol, m.p. 136° (lit.[32] 131–132°). ^1H n.m.r. δ 2·56 and 3·31, 2 t, *J* 7 Hz, 4H, CH_2CH_2NH; 3·38, s, 2H, $COCH_2Ph$; 3·85, s, 3H, OMe; 5·08, s, 2H, OCH_2Ph; 5·86, d, *J* 2 Hz, 2H, OCH_2O; 6·46–7·33, m, 11H, ArH.

1-(3-Benzyloxy-4-methoxybenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (25)

A mixture of 9·08 g (21·6 mmol) of the amide (24), 230 ml dried benzene and 19 ml $POCl_3$ was refluxed for 2 h. The residue obtained after evaporation to dryness was chromatographed on a Kieselgel 60 H column; elution with $CHCl_3/MeOH$ (92:8, v/v) furnished 8·23 g of the imine (25)[22] (yield 95%). ^1H n.m.r. δ 2·54, t, *J* 8 Hz, 2H, $(H4)_2$; 3·65, t, *J* 8 Hz, 2H, $(H3)_2$; 3·85, s, 3H, 4'-OMe; 3·91, br s, 2H, α-CH_2; 5·16, s, 2H, OCH_2Ph; 5·93, s, 2H, OCH_2O; 6·63 and 6·85, 2 s, 2H, H 8 and H 5; 6·85–7·54, m, 8H, ArH.

1-(3-Benzyloxy-4-methoxybenzoyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (26)

A solution of 8·1 g (20 mmol) of (25) in 120 ml of methanol was stirred and aerated at room temperature for 2 weeks. A pale yellow precipitate was formed which was collected and recrystallized from methanol. White crystals of the *keto imine* (26) (5·9 g) were thus obtained (yield 70%), m.p. 211° (Found: C, 72·1; H, 5·2; N, 3·5. $C_{25}H_{21}NO_5$ requires C, 72·3; H, 5·2; N, 3·4%). I.r. ν_{max} 1657 and 1590 cm^{-1}. ^1H n.m.r. δ 2·76, t, 2H, *J* 7·5 Hz, $(H4)_2$; 3·90, t, *J* 7·5 Hz, 2H, $(H3)_2$; 3·95, s, 3H, 4'-OMe; 5·21, s, 2H, OCH_2Ph; 5·96, s, 2H,

[32] Govindachari, T. R., Rajadurai, S., and Ramadas, C. V., *J. Sci. Ind. Res., Sect. B*, 1959, **18**, 533.

6,7-OCH_2O; 6·73, s, 1H, H5; 6·85, s, 1H, H8; 6·93, d, J_o 9 Hz, 1H, H5′; 7·30–7·61, m, 6H, ArH; 7·75, d, J_m 2 Hz, 1H, H2′.

1-(3-Benzyloxy-4-methoxybenzoyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide (27)

A solution of 4·53 g (10·9 mmol) of (26) in 175 ml acetone was filtered to remove insoluble matter, then treated with 15 ml methyl iodide and the mixture was heated on a water bath for 10 min. Yellow *crystals* (5·4 g) of the immonium iodide (27) (yield 89%) formed slowly on cooling, m.p. 214° (Me_2CO). ^1H n.m.r. δ 3·20–3·40 and 4·60–4·80, 2m, 4H, $(H4)_2$ and $(H3)_2$; 3·81, s, 3H, N^+Me; 4·00, s, 3H, 4′-OMe; 5·31, s, 2H, OCH_2Ph; 6·11, s, 2H, 6,7-OCH_2O; 6·65, s, 1H, H5; 6·91, s, 1H, H8; 7·16, d, J_o 8 Hz, 1H, H5′; 7·28–7·45, m, 6H, ArH; 7·56, d, J_m 2 Hz, 1H, H2′.

1-(3-Benzyloxy-α-hydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (28)

A solution of 4·2 g (7·55 mmol) of (27) in 400 ml of a $CHCl_3$/MeOH mixture (3:6, v/v) was reduced with sodium borohydride in the usual way. The reaction product was purified by chromatography on a Kieselgel 60 H column with $CHCl_3$/MeOH (95:5, v/v) for elution, then by crystallization from methanol. The amine (28) (3·75 g) was obtained as fine white *crystals* (yield 89%), m.p. 140° (MeOH). ^1H n.m.r. (C^2HCl_3 at 90 MHz), δ 2·46, s, 3H, NMe; 2·30–2·65 and 2·65–2·90, 2m, 4H, $(H4)_2$ and $(H3)_2$; 3·61, d, J 4·5 Hz, 1H, H1; 3·78, s, 3H, 4′-OMe; 4·85, d, J 4·5 Hz, 1H, Hα; 4·91, s, 2H, OCH_2Ph; 5·73, s, 2H, OCH_2O; 6·05, s, 1H, H8; 6·46, s, 1H, H5; 6·63–6·73 and 7·23–7·36 m, 8H, ArH.

1-(α,3-Dihydroxy-4-methoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline: threo *(29) and* erythro *(30) Isomers*

A solution of 600 mg of (28) in 20 ml of a mixture of benzene and concentrated hydrochloric acid (4:5, v/v) was refluxed for 2 h. After removal of the benzene, the acid aqueous phase was basified with 10% aqueous ammonia and extracted with chloroform. The organic extract was washed, dried (Na_2SO_4) and evaporated. A t.l.c. examination of the crude residue showed the presence of two products. Chromatography on a Kieselgel 60 H column with a $CHCl_3$/MeOH (88:12, v/v) mixture for elution allowed the two pure substances (29) (225 mg, 47% yield) and (30) (48 mg, 10% yield) to be separated. threo *Isomer* (29): pale yellow gum (Found: C, 66·2; H, 6·1; N, 4·1. $C_{19}H_{21}NO_5$ requires C, 66·5; H, 6·2; N, 4·1%). U.v. λ_{max} (log ϵ) 233 (3·86), 254 (4·52), 284 nm (3·60); after addition of 1 drop of aqueous NaOH, λ_{max} 245, 270, 294 nm. ^1H n.m.r. see Table 1. M.s. (c.i.) *m/z* 344 (M+1, 74%), 343 (M, 1), 326 (30), 192 (28), 191 (19), 190 (100), 189 (10), 188 (16), 153 (99), 152 (19). M.s. (e.i.) *m/z* 191 (13%), 190 (100), 189 (52), 188 (71), 153 (7), 152 (55), 151 (71). erythro *Isomer* (30): pale yellow gum (Found: C, 66·3; H, 6·2; N, 4·2. $C_{19}H_{21}NO_5$ requires C, 66·5; H, 6·2; N, 4·1%). U.v. identical with that of (29). ^1H n.m.r. see Table 1. M.s. (c.i.) *m/z* 344 (M+1, 86%), 343 (M, 1), 326 (34), 192 (7), 191 (12), 190 (100), 189 (10), 188 (3), 153 (38), 152 (5). M.s. (e.i.) *m/z* 191 (13%), 190 (100), 189 (2), 188 (5), 153 (1), 152 (5), 151 (6). The *erythro* compound (30) was likewise obtained in a yield of 65% by reduction of the keto immonium salt (32) with sodium borohydride under the usual conditions.

1-(3-Hydroxy-4-methoxybenzoyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (31)

The keto imine (26) (200 mg, 0·45 mmol) was dissolved in 5 ml of a mixture of ethanol and concentrated hydrochloric acid (1:1, v/v) which was refluxed for 2 h. After removal of the ethanol, the acid aqueous phase was basified with 10% aqueous ammonia and extracted with chloroform. The organic extract was washed, dried (Na_2SO_4) and evaporated. Chromatography on a Kieselgel 60 H column with a mixture of $CHCl_3$/MeOH (98:2, v/v) for elution furnished 108 mg (yield 69%) of pure (31), which crystallized from methanol in fine white needles, m.p. 211° (lit.[22] 211–212°). I.r. (KBr) ν_{max} 1645 cm^{-1}. ^1H n.m.r. δ (CF_3COO^2H at 60 MHz) 3·45, t, J 7 Hz, 2H, $(H4)_2$; 4·13, s, 3H, 4′-OMe; 4·23, t, J 7 Hz, 2H, $(H3)_2$; 6·18, s, 2H, 6,7-OCH_2O; 6·93, s, 1H, H5; 7·03, s, 1H, H8; 7·13, d, J_o 8 Hz, 1H, H5′; 7·58, dd, J_o 8, J_m 2 Hz, 1H, H6′; 7·68, d, J_m 2 Hz, 1H, H2′.

1-(3-Hydroxy-4-methoxybenzoyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium Iodide (32)

A mixture of 150 mg (0·46 mmol) of the phenolic keto imine (31), 3·5 ml of methanol, and 2 ml of methyl iodide was refluxed for 2 h. After evaporation to dryness, the residue was chromatographed on a column of Kieselgel 60 H; elution with a CH_2Cl_2/MeOH (90:10, v/v) mixture furnished 141 mg (89% yield) of the amorphous keto immonium iodide (32). ^{1}H n.m.r. δ (C^2HCl_3 at 90 MHz) 3·35, d, J 6 Hz, 2H, $(H4)_2$; 3·76, s, 3H, N^+Me; 3·96, s, 3H, 4′-OMe; 4·75, d, J 6 Hz, 2H, $(H3)_2$; 6·11 d, J 1·5 Hz, 2H, 6,7-OCH_2O; 6·66, s, 1H, H5; 6·95, s, 1H, H8; 7·08, d, J_o 9 Hz, 1H, H5′; 7·85, dd, J_o 9 Hz, J_m 2 Hz, 1H, H6′; 8·00, d, J_m 2 Hz, 1H, H2′.

1-(α,3-Dihydroxy-4-methoxybenzyl)-2,2-dimethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolinium Chloride: threo *Isomer (33) (Racemic Phyllocryptonine)*

To 100 mg (0·3 mmol) of the tertiary amine (29) (*threo* configuration) dissolved in 15 ml of acetone was added 10 ml of methyl iodide. The solution was warmed on a water bath at 30° for 10 min, then well stoppered and left overnight at room temperature. Evaporation of the solvent left a residue of iodide which was transformed into chloride by passage through a column of Amberlite IRA 400 (Cl^-) and elution with a mixture of Me_2CO/MeOH/H_2O (6:3:1, v/v). The pure quaternary ammonium chloride (33) (56 mg) was thus obtained (yield 53%) after crystallization from ether: fine white crystals, m.p. 189° (Et_2O); ^{1}H n.m.r. ($C^2H_3O^2H$ at 60 MHz) see Table 2. The product (33) was identical (co-t.l.c., i.r., ^{1}H and ^{13}C n.m.r., m.s.) with a sample of natural phyllocryptonine chloride (10).

1-(α,3-Dihydroxy-4-methoxybenzyl)-2,2-dimethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolinium Chloride: erythro *Isomer (34)*

The quaternization of 100 mg of the tertiary amine (30) with methyl iodide, followed by transformation of the iodide into chloride, was carried out as for the preparation of the *threo* isomer (33) described above; 39·5 mg (38%) of the pure amorphous quaternary ammonium chloride (34) were obtained. U.v. identical to that of (33). ^{1}H n.m.r. ($C^2H_3O^2H$ at 60 MHz) see Table 2. M.s. (c.i.) *m/z* 358 (M, 14%, $C_{20}H_{24}N^+O_5$), 344 (22), 326 (2), 193 (13), 192 (100), 170 (79), 153 (47). M.s. (e.i.) *m/z* 343 (2%), 341 (2), 191 (45), 190 (77), 153 (2), 152 (73), 151 (84), 148 (100).

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