THE INDOLIZIDINE ALKALOIDS

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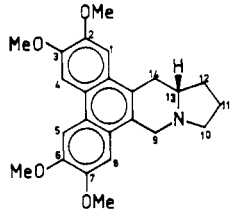
The indolizidine ring system is present in many alkaloids isolated from plant species of different families. However, a number of these alkaloids have already been classified as members of other alkaloid groups because structural or biogenetic considerations indicated preference towards another heterocyclic system. Consequently, alkaloids containing an indolizidine ring system can be found among the Amaryllidaceae (cancentrine) and *Erythrina* (indole and mesembrine alkaloids). This review deals with alkaloids in which the indolizidine ring is the dominant heterocyclic system, *i.e.*, those isolated from plant species belonging to the families of Asclepiadaceae, Convolvulaceae, Moraceae, Orchidaceae, the fungus Rhizoctonia and from animal sources. The Elaeocarpaceae (1) and *Securinega* (2) alkaloids are not discussed here, although they belong to the indolizidine alkaloids, as they have been reviewed in the not too distant past. The indolizidine alkaloids can be divided into two major groups, the phenanthroindolizidines from the Asclepiadaceae and Moraceae families and the simpler indolizidines from all other sources.

PHENANTHROINDOLIZIDINE ALKALOIDS

Phenanthroindolizidine alkaloids have been isolated from only two plant families. Their presence has been established in several species of five genera, *Tylophora*, *Cyanchum*, *Vincetoxicum*, *Pergularia* and *Antitoxicum* among the more than 300 genera of the Asclepiadaceae family (3) and in one species of the genus *Ficus* of the Moraceae family (4).



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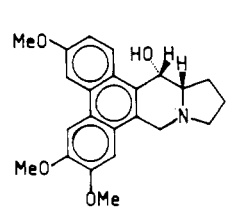

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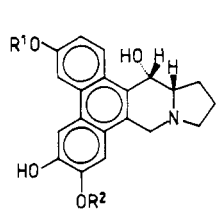
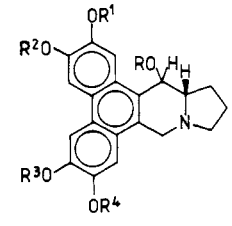


3 either R^1=H; R^2=Me
or R^1=Me; R^2=H



4 R=OH; R^1, R^2, R^3, R^4=2×H+2Me

6 R^1=R^2=Me

5 R=H; R^1, R^2, R^3, R^4=H+3Me

1. ISOLATION OF THE ALKALOIDS

A. *The Asclepiadaceae Family*

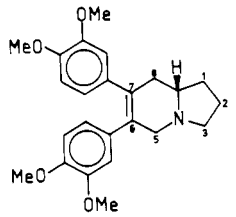
a. The genus *Tylophora*

Of some 50 species of this genus (5–8), which are well distributed all over Africa, Asia, Australia and the Pacific Islands, 23 have been reported to contain alkaloids (8,9,10). However, only from a few of these species have alkaloids been isolated and characterized.

T. indica, (Burm) Merrill previously known as *T. asthmatica*, Wight et Arn.—The presence of alkaloids in this species was first recorded in 1891 by Hooper (11) and also by Arata and Gelzer (12). The two inadequately characterized alkaloids were reisolated by Ratnagirisvaran *et al.* (13) who named them tylophorine (**1**) and tylophorinine (**2**). Although Chopra *et al.* (14–16) could isolate only tylophorine and an unidentified base (which may be identical with septicine), the systematic work carried out by Govindachari *et al.* (17) confirmed the presence and identity of Ratnagirisvaran's alkaloids. Rao (18), in his patent, described the isolation of five alkaloids, viz., compound A (identical with tylophorine), B (identical with tylophorinine), C (a desmethyltylophorinine) (**3**), D (**4**), E, and a trace of a sixth, unidentified alkaloid. Subsequently, Rao *et al.* (19) reported the isolation of five alkaloids: tylophorine, tylophorinine, Alkaloid *A* (**4**) (compound D of the patent), Alkaloid *B* (identified as a desmethyltylophorine) (**5**), and Alkaloid *C* (a 3- or 6-desmethyltylophorinine), which was shown later to be identical with tylophorinidine (**6**), (20), and not identical with compound C (**3**) of the patent. Mulchandari *et al.* (21) isolated tylophorinidine (**6**), and Govindachari *et al.* (20) isolated (+)-septicine (**7**), and (+)-isotylocrebrine (**8**). Tylophorine, tylophorinine and some unidentified and uncharacterized minor alkaloids were also isolated from Sri Lankan species (8). Finally, Govindachari *et al.* (22) also isolated three quaternary alkaloids, dehydrotylophorine (**9**), anhydrodehydrotylophorinine (**10**), and anhydrodehydrotylophorinidine (**11**), as their perchlorates. However, due to the easy aerial oxidation of these alkaloids, they may be artifacts formed during the isolation process (22).

T. crebriflora S. T. Blake.—The isolation of the alkaloids (−)-tylocrebrine (**12**), (23,24) and tylophorine (**1**) was reported in 1962. Later Rao *et al.* (25,26) described the isolation of six more alkaloids, viz., alkaloids *A* (**13**), *B* (**14**), *C* (**15**), *D* (**16**), *E* (**17**) and Alkaloid F, identified later as the secophenanthroindolizidine alkaloid septicine (**7**).

T. dalzellii Hook f.—The isolation of a demethyltylophorinine and compound E, of the patent was reported by Rao (18) and Rao *et al.* (19).



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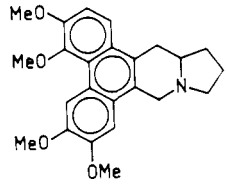

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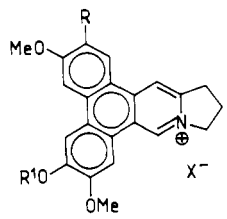
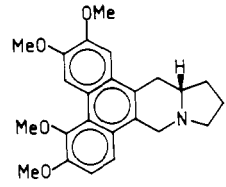


9 R=OMe; R¹=H

10 R=H; R¹=Me

11 R=R¹=H



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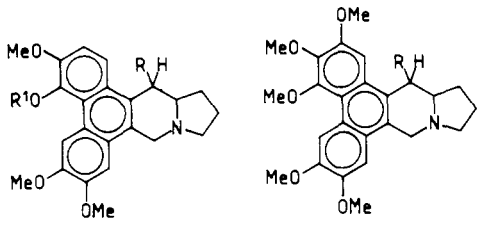
Other *Tylophora* species.—Brill *et al.* (27) reported the presence of one of Hooper's unidentified alkaloids in *T. brevipes* (Turcz.) F.-Villar. Screening data indicate the presence of indolizidine alkaloids in the following species: *T. sylvatica* Decne (6,28), *T. erecta* F. Muell. ex Benth. (7), *T. hirsuta* Wight (10,29), *T. flava* Trimen (8), *T. cordifolia* Thw (8, 10), *T. capparidifolia* Wight et Arn. (10), *T. exelis* Coleb (10), *T. fasciculata* Ham (10), *T. govani* Done. (10), *T. iphisia* Done. (10), *T. longifolia* Wight (10), *T. macrantha* Hook f. (10), *T. mollissima* Wight (10), *T. pauciflora* Wight et Arn. (10), *T. rotundifolia* Ham. (10), *T. tenerrima* Wight (10), *T. tennis* Blume (10), *T. zeylamia* Done. (10), and *T. paniculata* R. Br. (7).

b. The genus *Vincetoxicum*

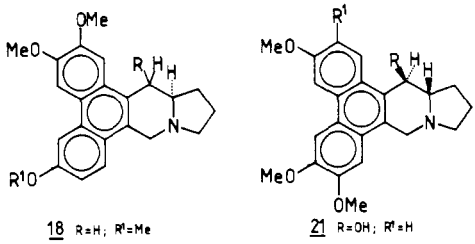
Pailer and Streicher (30) isolated from *V. officinale* Moench. tylophorine and a second alkaloid which is probably identical with (−)-antofine (**18**), isolated, but not characterized, earlier by Platonova *et al.* (31).

c. The genus *Cyanchum*

Haznagy *et al.* (32,33) showed, by tlc, the presence of three alkaloids in *C. vincetoxicum* (L.) Pers. and named one of them substance C-1 (34). Later, Wiegrebe *et al.* (35) isolated tylophorine and two other alkaloids, viz., 2,3,6-trimethoxy-9,11,12,13,13a,14-hexahydrodibenzo



13 R=OH; R¹=Me
14 R=R¹=H
15 R=OH; R¹=H
16 R=OH
17 R=H

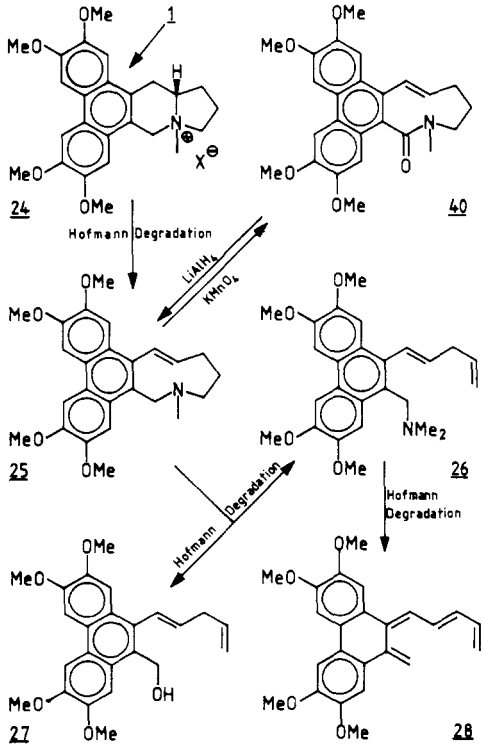


18 R=H; R¹=Me
19 R=R¹=H
20 R=OH; R¹=Me
21 R=OH; R¹=H
22 R=R¹=H
23 R=OH; R¹=OMe

[f,h]pyrrolo-[1,2-b]isoquinoline (**18**) (Alkaloid A, which is identical with substance C-1 of Haznagy *et al.* (34), the second alkaloid of Pailer *et al.* (30), and antofine of Platonova *et al.*) (31), and alkaloid C, **19**. The 14-hydroxy derivative of alkaloid A, **20**, was also isolated by Wiegrebe *et al.* (36).

d. The genus *Pergularia*

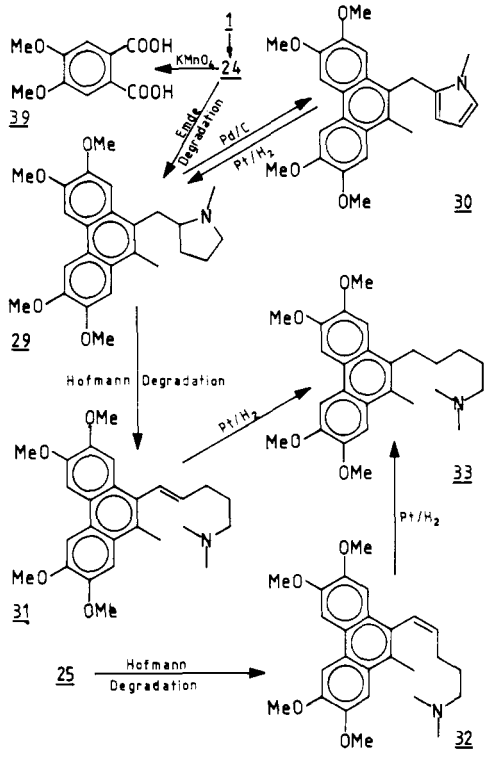
Mulchandari *et al.* (37–39) reported the isolation of tylophorine, tylophorinidine, pergularinine (**21**), desoxypergularinine, **22**, and another alkaloid of M^+409, **23**, $C_{24}H_{27}NO_5$, from *P. pallida* Wight et Arn.



24 25 26 27 28 40

e. The genus *Antitoxicum*

Platonova *et al.* (31) have isolated antofine (**18**), from *Antitoxicum funebre* Boiss and Kotschy.



B. The Moraceae Family

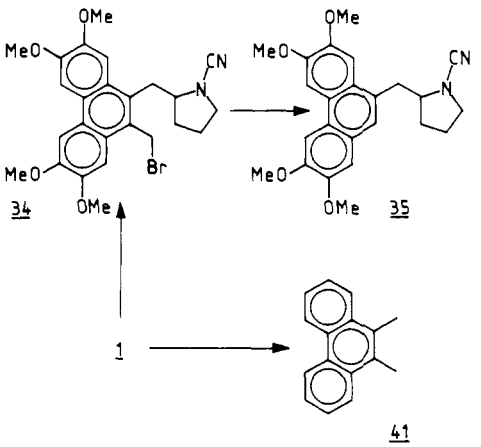
Only one species of the genus *Ficus* is known to contain indolizidine alkaloids. Russell (4) isolated (−)-tylophorine (**1**), (−)-tylocrebrine (**12**), and (−)-septicine (**7**), from *F. septica* Forst. f., while Herbert *et al.* (40) found partially racemic antofine (**18**) as its major alkaloid.

2. Structures of the phenanthroindolizidine alkaloids

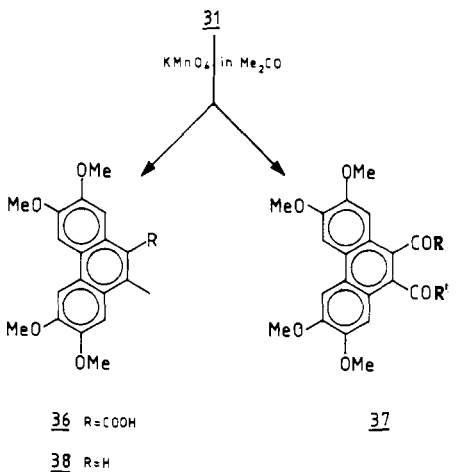
Tylophorine (**1**), $C_{24}H_{27}NO_4$, contains four methoxyl groups, no N-methyl, C-methyl or carbonyl groups, no readily reducible double bonds, and no active hydrogen atoms showing that the nitrogen is tertiary. Its uv spectrum shows maxima at 255, 290, 340, and 352 nm indicating a substituted phenanthrene ring system. Tylophorine methiodide (**24**, $X^-=I^-$) gives, on boiling with alkali, the racemic tylophorine methohydroxide (**24**, $X^-=^-OH$), instead of a methine, and can be reconverted into the racemic isomethiodide, as was reported in case of the phenanthroquinolizidine alkaloid, cryptopleurine by Gellert *et al.* (42) and Gellert (43,44). Hofmann degradation of tylophorine established that the nitrogen atom is common to two rings. Tylophorine-methine-I (**25**), $C_{25}H_{29}NO_4$, yielded, on a second Hofmann-degradation tylophorine-methine-II, $C_{26}H_{31}NO_4$ (**26**) and an *N*-free product (**27**), $C_{24}H_{24}O_5$, representing the displacement of the benzylic dimethylamino group by an OH group. Hofmann degradation of tylophorinemethine-II (**26**), yielded tylophorine-methine-III, $C_{24}H_{22}O_4$ (**28**). Attempted hydrogenation of tylophorine-methine-I yielded the racemic tylophorine methohydroxide (**24**, X=OH) instead of the dihydro compound. Such conversion of a methine to the original quaternary base has been shown by Pyman (45) to occur in the case of dibenzoquinolizidine alkaloids, *e.g.*, canadine.

Emde degradation of tylophorine methochloride (**24**, $X^-=^-Cl$) yielded isodihydrohomotylophorine (**29**), $C_{25}H_{31}NO_4$, which could be dehydrogenated with Pd/C to the tetradehydro derivative (**30**), $C_{25}H_{27}NO_4$, containing a pyrrole ring. This latter compound rehydrogenated to isodihydrohomotylophorine which confirmed the presence of a pyrrolidine ring in the Emde product (46). Hofmann degradation of isodihydrohomotylophorine gave a methine (**31**), $C_{26}H_{33}NO_4$, which is different from the Emde degradation product (**32**), $C_{26}H_{33}NO_4$, obtained from tylophorine-methine-I (**25**). As both compounds hydrogenated to the same isotetrahydrohomotylophorine methine (**33**), $C_{26}H_{35}NO_4$, they must be geometrical isomers (47), as shown in formulae **31** and **32**.

Tylophorine gave a bromocyanamide (**34**), $C_{25}H_{27}N_2O_4Br$, which was reduced by $NaBH_4$ to a hydroxycyanamide (**35**), $C_{25}H_{28}N_2O_5$. The latter regenerated tylophorine on acid hydrolysis, which was only possible in the presence of a 1,4- or 1,5-aminoalcohol grouping in the hydroxycyanamide.



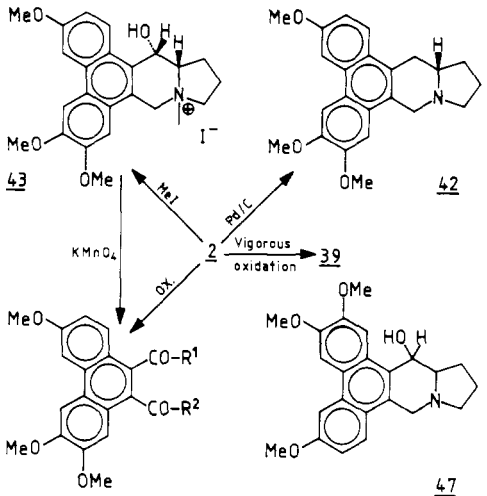
Oxidation of **31** with $KMnO_4$ in acetone (46) yielded the esters of two acids, a mono- (**36**, R=COOH) and a dicarboxylic acid (**37**, $R=R^1=OH$), which were separated from each other by chromatography of their methyl esters. The methyl ester of **36** (R=COOMe) gave, on hydrolysis followed by decarboxylation, 2,3,6,7-tetramethoxy-9-methylphenanthrene (**38**). The ester of **37**, ($R=R^1=OMe$), was hydrolyzed and identified through its anhydride **37**, ($R+R^1=O$) and imide **37**, ($R+R^1=NH$) as the 2,3,6,7-tetramethoxyphenanthrene-9,10-dicarboxylimide. It could also be obtained by $KMnO_4$ oxidation of the racemic isotylophorine methohydroxide (**24**, $X=OH$) either in pyridine or in aqueous pyridine solution. Oxidation of tylophorine methiodide (**24**, X=I) with aqueous $KMnO_4$ at 100° gives *m*-hemipinic acid (**39**); while $KMnO_4$ oxidation of tylophorine-methine-I (**25**), either in acetone or pyridine, yielded a neutral product (**40**), $C_{25}H_{27}NO_5$, obviously a lactam since $LiAlH_4$ in the THF reconverted it to the starting material.



Zinc dust distillation (48) of tylophorine yielded 9,10-dimethylphenanthrene (**41**), establishing that the fusion of the indolizidine ring to the phenanthrene ring was in the 9,10-position.

Tylophorinine (**2**), (49,50), $C_{23}H_{25}NO_4$, has three methoxyl groups, no N-methyl, C-methyl or carbonyl groups, no readily reducible double bond but an alcoholic hydroxy group established by ir spectroscopy. Its uv spectrum shows maxima at 258, 287 and 340 nm, very similar to that of cryptopleurine (42), a 2,3,6-trimethoxyphenanthrene derivative. No useful degradation products were isolated from attempted Hofmann and Emde degradations, but hydrogenolysis in acetic acid-perchloric acid solution with Pd/C gave desoxytylophorinine (**42**), $C_{23}H_{25}NO_3$. Vigorous oxidation of the alkaloid gave *m*-hemipinic acid (**39**) in very low yield as the only identifiable product, but mild oxidation of the methiodide (**43**) yielded a dicarboxylic acid (**44**) and its imide (**45**), $C_{19}H_{15}NO_5$, identified as 2,3,6-tri-methoxyphenanthrene-9,10-dicarboxylic acid and isolated as its dimethyl ester (**46**), $C_{21}H_{20}O_7$. As these reactions indicated that tylophorinine possessed a phenanthroindolizidine skeleton, the hydroxy group could be placed on C-14. The non-symmetric position of the nitrogen atom relative to the methoxyl substituents allowed for two alternative structures, **2** and **47**. That the structure of tylophorinine is represented by the (−)-isomer of **2** was established at a later date (51) after synthesis of both isomers and comparison of the synthetic and natural materials.

The levorotatory tylocrebrine (**12**), $C_{24}H_{27}NO_4$, (24) contains four methoxyl groups, no N-methyl, C-methyl or carbonyl groups, no readily reducible double bonds or active hydrogen



44 $R^1=R^2=OH$

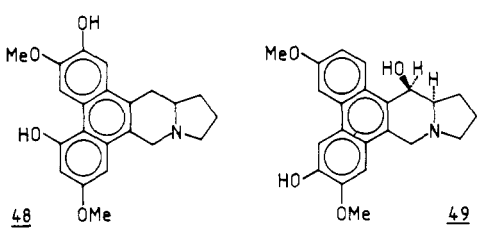
45 $R^1+R^2=NH$

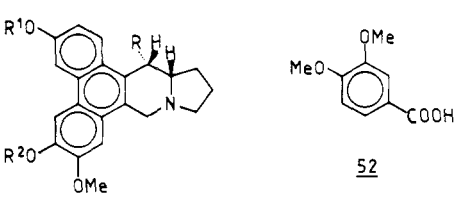
46 $R^1=R^2=OMe$

atoms. Its uv spectrum shows absorption maxima at 263, 342 and 360 nm and is practically superimposable on that of 3,4,6,7-tetramethoxy-9-methylphenanthrene. The alkaloid is isomeric with tylophorine (**2**), from which it differs only in the position of a methoxyl group giving rise to two alternative structures **12** and **8**. That the structure of tylocrebrine is represented by **12** and that of isotylocrebrine by **8** was confirmed by the synthesis of both isomers and comparison with the alkaloids.

The levorotatory antofine (**18**), $C_{23}H_{25}NO_3$, (30,31) contains three methoxyl groups, no N-methyl, C-methyl or carbonyl groups, and no readily reducible double bonds or active hydrogen atoms. Its uv spectrum shows absorption at 256, 284, 341 and 354 nm and is practically superimposable on that of tylophorine. Its structure is represented by **18**, an isomer of **42**, which had been synthesized earlier (52).

Of the three alkaloids isolated from *T. asthmatica* described in Rao's patent (18), compound C (**3**), $C_{22}H_{23}NO_4$, is identical with Rao's Alkaloid B (19) and is a nortylophorinine since it yielded **2** on methylation. Compound D (**4**), identical with Rao's Alkaloid A, $C_{22}H_{23}NO_5.H_2O$, is likely to be 14-hydroxybisdesmethyltylophorine, while the structure of compound E, probably $C_{23}H_{25}NO_4.\frac{1}{2}H_2O$, is not known. Rao's alkaloid C (19), which is not identical with his compound C, is either a 3- or 6-desmethyltylophorinine. Later, however, it was proposed to be the hydrated form of tylophorinidine (**6**), not its isomer (20).





50 R=OH; $R^1=R^2=Me$

51 $R=R^2=H$; $R^1=Me$

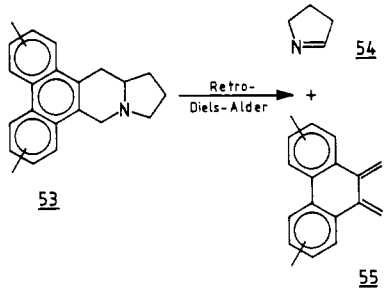
Tylophorinidine (**6**), $C_{22}H_{23}NO_4$, (21) was originally assigned structure **48** but was corrected to **49** (2) then to its enantiomer **6**, (53) which is 6-de-*O*-methyltylophorinine. This assignment was confirmed by methylation of **6** to **2**, and showed that *O*-methylated-**6** (**50**) and **2** gave the same **42** on hydrogenolysis.

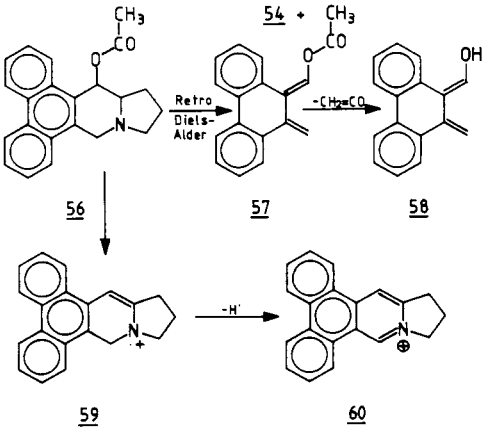
The structures of the quaternary alkaloids were established by catalytic reduction to the corresponding tertiary alkaloids. Dehydrotylophorine reineckate (**9**) gave (±)-**2** on hydrogenation, while its mother liquors containing anhydrohydrotylophorinine and anhydrodehydrotylophorinidine reineckates, **10** and **11**, gave a mixture of (±)-desoxytylophorinine (**42**) and (±)-desoxytylophorinidine (**51**).

Of Rao's alkaloids (25,26) isolated from *T. crebriflora*, alkaloid A (**13**), $C_{24}H_{27}NO_5$, showed the same pattern of methoxy substitution as tylocrebrine. Hydrogenolysis yielded isotylocrebine (**8**). It is, therefore, 14-hydroxyisotylocrebrine. Alkaloid B (**14**), $C_{23}H_{25}NO_4$, contains one phenolic hydroxy and three methoxyl groups and methylates to **8**. It is, therefore, desmethylisotylocrebrine. Alkaloid C (**15**), $C_{23}H_{25}NO_5$, contains one phenolic and one alcoholic OH and three methoxyl groups; it methylates to **13** and on hydrogenolysis yielded **14**. Therefore, **15** is desmethyl-alkaloid A. The nmr spectra of alkaloids A and C differ significantly only in an upfield shift (25 cps) of the signal due to the C-5 proton of the phenanthrene ring, a difference which disappears on acetylation. This restricts the position of the phenolic OH group in alkaloids B and C to C-4 or C-6. The positive Gibbs test, which requires a free *para* position to the phenolic OH, established that the phenolic OH is on C-4. Alkaloid D (**16**), $C_{25}H_{29}NO_6$, contains one alcoholic OH and five methoxyl groups and gave, on Clemmenson reduction, alkaloid E (**17**), $C_{25}H_{29}NO_5$. This transformation established the identical pentamethoxy substitution pattern of the two alkaloids and the presence of a 14-hydroxy group in the former. The similarity of their nmr spectra to that of tylocrebrine indicated a 2,3,6,7 or a 3,4,7,8 substitution pattern. In addition, the absence of *ortho* aromatic protons suggested that the fifth methoxy group was located on either C-2 or C-8. The fact that, due to the presence of an OH group on C-14, the signal for one aromatic proton in alkaloid C (**20**) is shifted downfield when compared with alkaloid B (**14**), placed the fifth methoxyl group on C-2.

(−)-Pergularinine (**21**), $C_{23}H_{25}NO_4$, (37,38,39) was shown to be a diastereoisomer of O-methyltylophorinidine (**49**). As desoxypergularinine (**22**), showed in ord studies a negative Cotton effect of the same magnitude as tylophorine (**1**), the configuration at C-13a must be the same as in **1**, **6**, **21**, **50**, and **51**. This establishes that pergularinine and *O*-methyltylophorinidine differ from each other only in their configuration at C-14. The structure of alkaloid D, M^+409, $C_{24}H_{27}NO_5$, from *P. pallida* is probably 14-hydroxytylophorine (**23**), but this tentative structure has not yet been confirmed.

The structure of the *seco*-phenanthroindolizidine alkaloid, septicine (**7**), $C_{24}H_{29}NO_4$, was established by oxidation of its methiodide to veratric acid (**52**), and by its transformation through uv irradiation (4) to a mixture of tylocrebrine and tylophorine.





Mass spectral fragmentation of phenanthroindolizidine alkaloids, *e.g.*, (**53**) takes a different path depending on whether C-14 is oxygenated or not. Without a C-14 hydroxyl group, fragmentation proceeds *via* the *retro*-Diels-Alder reaction (3,21,54) and produces 1,2-dehydropyrrolidine (**54**), together with substituted 9,10-dimethylenephenanthraquinone derivatives (**55**), showing that in all known phenanthroindolizidine alkaloids the pyrrolidine portion of the alkaloids is unsubstituted. The *retro*-Diels-Alder reaction of the acetates of C-14 hydroxylated alkaloids, *e.g.*, (**56**) (36,54) yields **54** and **57** (acetylated **55**), which loses ketene to yield **58**, followed by the loss of CO. The main fragmentation of the 14-acetoxy compound (**56**) proceeds, however, by McLafferty rearrangement initiated by the loss of acetic acid to **59**, followed by the formation of the stable dibenzoisoquinolinium ion (**60**), which further fragments by the loss of HCN.

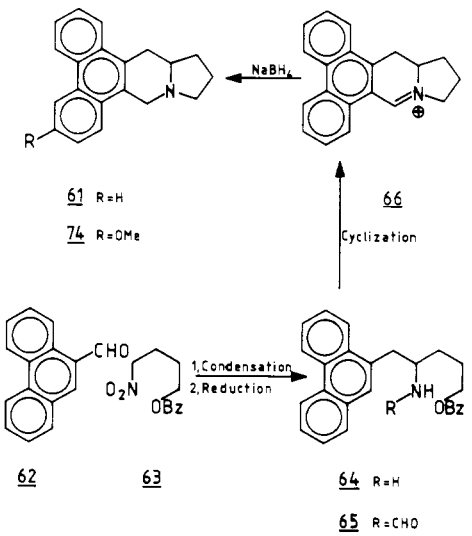
The nmr spectra of the alkaloids cannot unequivocally distinguish between, *e.g.*, 2,3,6- or 3,6,7-trimethoxy substituted phenanthrene derivatives so that structure elucidations were confirmed by synthesis of the two alternative structures initially proposed. Later, however, it was shown (54) that the presence of an oxygen function in the C-14 position either as hydroxy (26) or acetate (36) or the introduction of the magnetically strongly anisotropic cyano group at C-9 (35,54) produced sufficient deshielding of the neighboring aromatic protons to enable the complete assignment of the substitution.

The absolute configuration of antofine (**18**), and 6-*O*-demethyl-antofine (**19**), was established by Wiegrebe *et al.* (55).

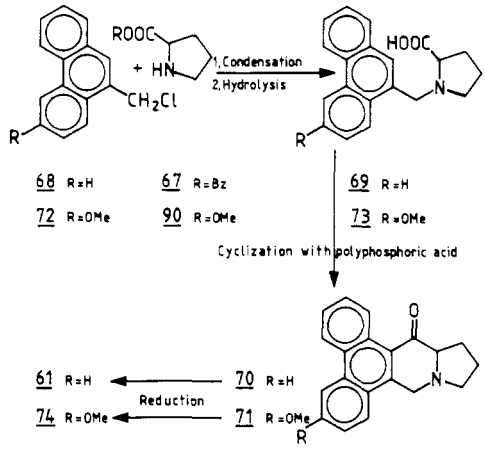
Ozonolysis in dilute formic acid of both alkaloids gave *D*-proline (*R*-configuration) identified by enzymatic analysis using *D*-amino acid oxidase. Later a stereospecific synthesis (56,57) established that C-13a of the two alkaloids has the *R*-configuration. Ozonolysis (58) of (−)-tylophorine (**1**), as above, gave *L*-proline identified by gc. Comparison (59,60) of its methyl *N*-trifluoroacetyl prolinate derivative with authentic material pointed to the *S*-configuration. As the signs of the Cotton effects in the ord curve of tylophorine (**1**) are opposite to those of antofine (**18**), it is suggested that (+)-isotylocrebrine (**8**) with an ord curve similar to that of antofine also has the *R*-configuration at C-13a. Tylophorinidine (**6**) was initially assigned the absolute configuration **48** (20), but this was changed to **6** (53) after X-ray analysis, which also established the absolute configuration of desoxytylophorinidine (50). The absolute configuration of (−)-tylocrebrine (**12**) was established as *S* by comparison of the ord spectra of tylophorine and cryptopleurine with that of tylocrebrine (61,62). The absolute configuration of septicine was determined as **7** by the stereo-specific synthesis of Russell *et al.* (63).

3. Syntheses of the phenanthroindolizidine alkaloids

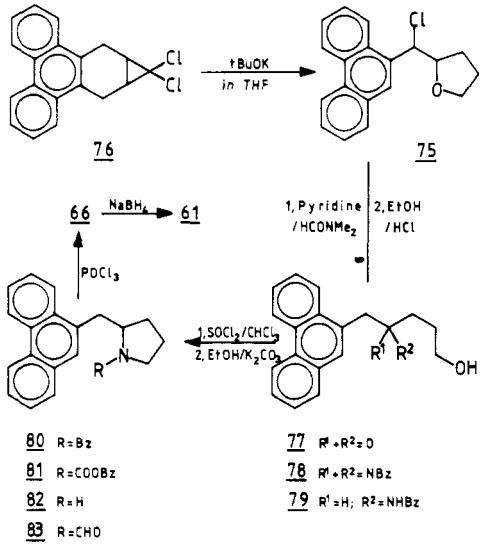
The unsubstituted molecule.—The methods devised by Bradsher and Berger (64,65) and by Marchini and Belleau (66) for the synthesis of phenanthroquinolizidines were adopted for the synthesis of phenanthroindolizidines. The basic skeleton (**61**, R=H) was first synthe-



sized by Govindachari *et al.* (41). They condensed phenanthrene-9-aldehyde (**62**) with ω-nitrobutyl benzoate (**63**) and reduced the product with lithium aluminium hydride to **64** (R=H), which was formylated to yield **65** (R=CHO) then cyclized to **66** and hydrogenated to **61**. Chauncy *et al.* (67) condensed benzyl *L*-prolinate (**67**) with 9-phenanthrylmethyl chloride (**68**) and hydrolyzed the product to the corresponding acid (**69**, R=H), which was cyclized to the racemic phenanthroindolizidone (**70**, R=H) with polyphosphoric acid and reduced either by a modified Wolff-Kishner reaction or by sodium dihydrobis (2-methoxyethoxy) aluminate (68) to **61**. Similarly the 6-methoxyderivative (**71**, R=OMe), prepared from **67** and **72** *via* **73**, was reduced to 6-methoxyphenanthroindolizidine (**74**, R=OMe). More recently, Takano *et al.* (69) synthesized 9-(chloro-2-tetrahydrofurylmethyl)-phenanthrene (**75**) by reacting 7,7-dichloro-dibenzo[a,c] bicyclo [4.1.0] heptane (**76**), prepared from phenanthrene and dichlorocarbene,

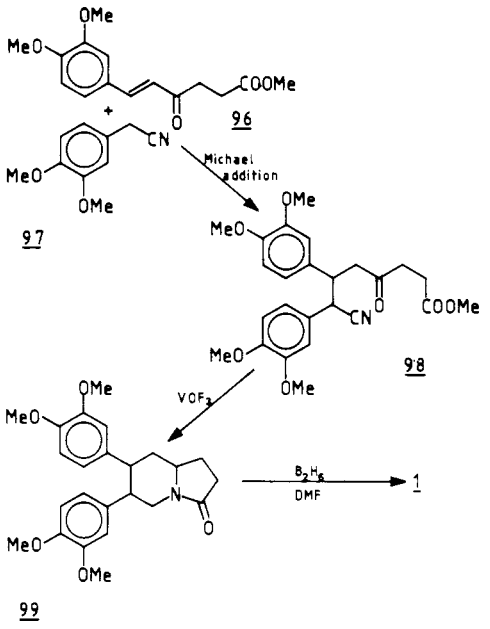


with potassium *t*-butoxide in THF. Dehydrochlorination of **75** with pyridine in dimethyl formamide followed by hydrolysis with alcoholic hydrochloric acid gave the ketol (**77**), which was converted to the benzylamino alcohol (**78**), by reduction with sodium borohydride of its Schiff-base (**79**). Reacting **78** with thionyl chloride in chloroform followed by stirring with alcoholic potassium carbonate gave the *N*-benzylpyrrolidine (**80**, R=Bz). This was converted to the carbamate (**81**, R=COOBz) with carbobenzoxychloride in presence of $KHCO_3$ in chloroform; **81** then gave, on heating with alcoholic hydrochloric acid, the pyrrolidine derivative (**82**, R=H). *Cyclization of the formyl derivative* (**83**, R=CHO) *with phosphorous oxychloride* followed by reduction of the product (**66**) with sodium borohydride gave **61**.

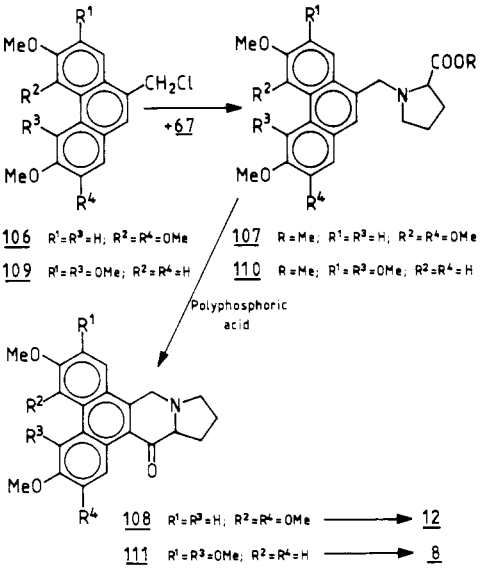


Tylophorine (**1**).—Condensation of 2,3,6,7-tetramethoxy-9-chloromethyl phenanthrene (**84**) with pyrryl magnesium bromide gave the pyrrole derivative (**85**), which was reduced to **86** then *N*-formylated to **87**. Ring closure with $POCl_3$ afforded the quaternary phenanthroindolizideine salt (**88**), which was reduced by $NaBH_4$ to racemic tylophorine (**1**) (70). Resolution of (±)-**1** with (+)-camphor-10-sulphonic acid produced both the (+)- and (−)-isomers. In other syntheses of **1** (71,72), methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate (**89**) was condensed with methyl prolinate (**90**) to yield an amide (**91**), which could be reduced under the conditions specified by Borch (73) to **92**. Hydrolysis to **93** and cyclization with polyphosphoric acid gave the aminoketone **94**, which yielded (±)-**1** *via* either Clemmenson reduction (71) or $NaBH_4$, reduction of the tosylhydrazone. Hydrogenolysis (71) of **94** gave only the corresponding alcohol **95**. Liepa *et al.* (74) condensed veratraldehyde and levulinic acid to produce **96**. This material underwent Michael addition with 3,4-dimethoxybenzylcyanide (**97**) to yield **98**. Cyclodehydration of **96** with vanadyl trifluoride converted the cyanoketoester to the lactam (**99**). Excess diborane gave an adduct with **99**, which could be cleaved to (±)-**1** by heating in DMF.

Tylophorinine (**2**).—Synthesis of **2** followed the second method employed for **1**. It commenced with **100** and proceeded through the appropriately substituted intermediates **101**,

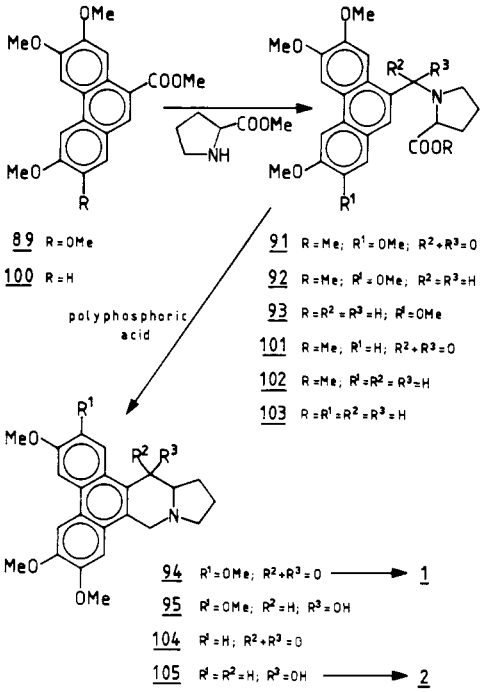


102, **103**, **104** to **105**, which was reduced by sodium borohydride to a mixture from which **2** was isolated (51).

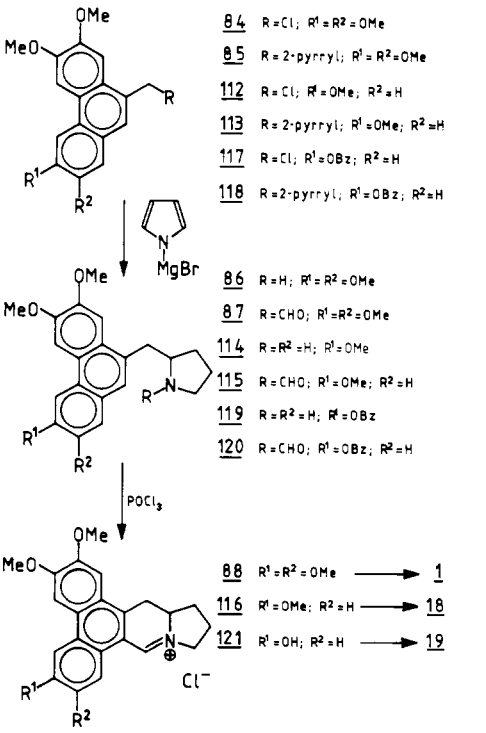


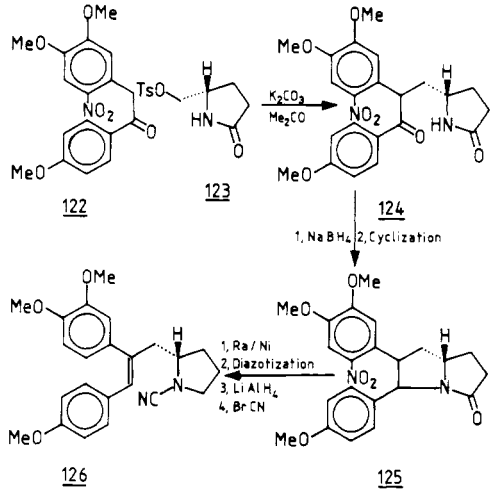
Tylocrebrine (**12**) and *Isotylocrebrine* (**8**).—Condensation (72) of 9-chloromethyl-3,4,6,7-tetramethoxyphenanthrene (**106**) with benzyl prolinate (**67**) in methanol yielded the transesterified product **107**, which was hydrolyzed to the acid and cyclized with the aid of polyphosphoric acid to **108**. The tosylhydrazone of this aminoketone was then reduced to (±)-tylocrebrine (**12**). Similarly, condensation (72) of 9-chloromethyl-2,3,5,6-tetramethoxyphenanthrene (**109**) with **67**, as above, yielded **110**, which gave, *via* **111**, (±)-isotylocrebrine (**8**).

Antofine (**18**) and Wiegrebe's Alkaloid *C* (**19**).—Alkaloids **18** and **19** were synthesized from appropriately substituted chloromethylphenanthrenes *via* the earlier recorded pyrrole condensation method (75). 9-Chloromethyl-2,3,6-trimethoxyphenanthrene (**112**) was converted to its 2-pyrryl derivative (**113**) and reduced to the pyrrolidine derivative **114**. Formylation afforded **115**, which could be cyclized with phosphorus oxychloride to **116** and reduced to (±)-antofine (**18**). Similarly, 9-chloromethyl-6-benzyloxy-2,3-dimethoxyphenanthrene (**117**) was converted through **118**, **119**, **120** to **121**, which was reduced and hydrogenolyzed to the racemate of Wiegrebe's alkaloid *C* (**19**). It should be noted that, during hydrogenation of **118** to **119**, some debenzylation also occurred; but the free phenolic hydroxy group generated by this did not interfere with the Bischler-Napieralski ring closure (76). The stereospecific

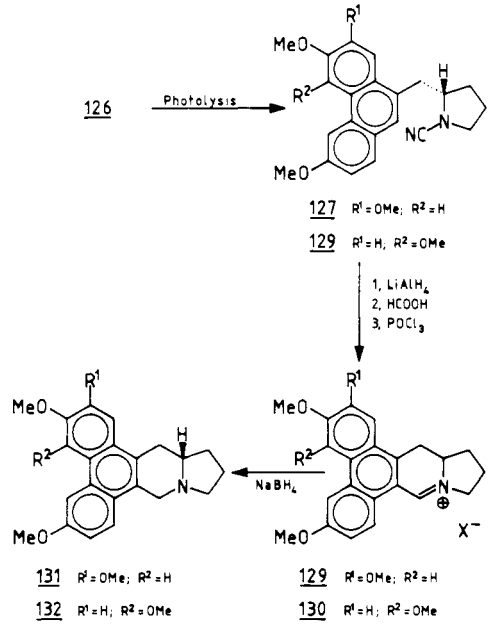


synthesis (56,57) of the *S*-(+) isomer of *R*-(−)-**18** was established by alkylation of 4,4',5'-trimethoxy-2'-nitrodesoxybenzoin (**122**) with (*S*)-(2-pyrrolidon-5-yl)methyl-*p*-toluenesulphonate (**123**) to **124**. This ketopyrrolidone was reduced with $NaBH_4$ to the hydroxypyrrolidone derivative, which was dehydrated and cyclized to **125**. Reduction of the nitro group to an amino group and its replacement by hydrogen was followed by the opening of the pyrrolizidine ring with BrCN and dehydrobromination to **126**. Photolysis of **126** gave a mixture of **127** (R^1=OMe; R^2=H) and **128** (R^1=H; R^2=OMe). Both were reduced by $LiAlH_4$ to the corresponding amines, then formylated and cyclized, respectively, to **129** and **130**. Separation





followed by $NaBH_4$ reduction gave **131**, the (*S*)-(+)-isomer of **18**, and the (*S*)-(+)-3,4,6-trimethoxyphenanthroindolizidine (**132**). Recently, antofine has been synthesized also by the directed metalation of tertiary benzamide method of Snieckus (77).



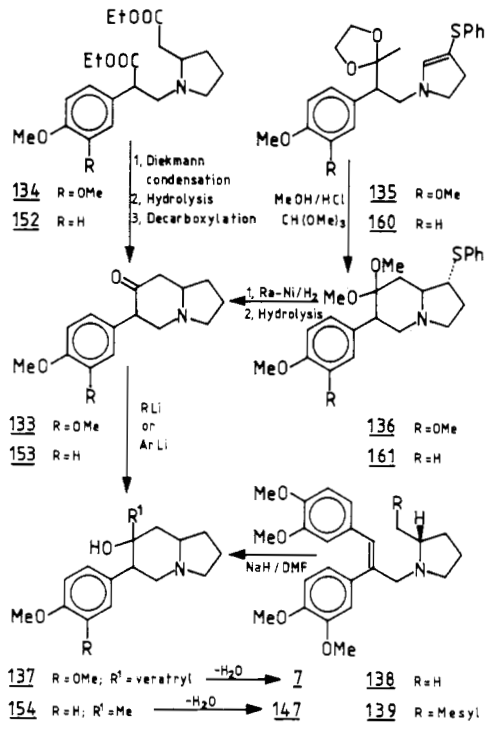
Septicine (**7**).—The racemic alkaloid (78) was synthesized from **133**. This was prepared either by *N*-alkylation of ethyl 2-pyrrolidinyl acetate with ethyl 2-(3,4-dimethoxyphenyl)-3-chloropropionate to **134**, followed either by Dieckmann condensation to **133**, or by ring closure (79) of **135** to **136**, and desulphurization and hydrolysis of the ketal. Reaction of the aminoketone **133** with veratryl lithium gave an aminoalcohol **137**, which could be dehydrated with $KHSO_4$ to (±)-**7**.

A stereospecific synthesis of (−)-**7** (63) was achieved by condensing 2,3-di-(3,4-dimethoxyphenyl)-allyl chloride with *L*-prolinol to **138** (R = H) then reacting its mesylate **139** (R = mesyl) with sodium hydride in dimethyl formamide to yield (−)-**7**.

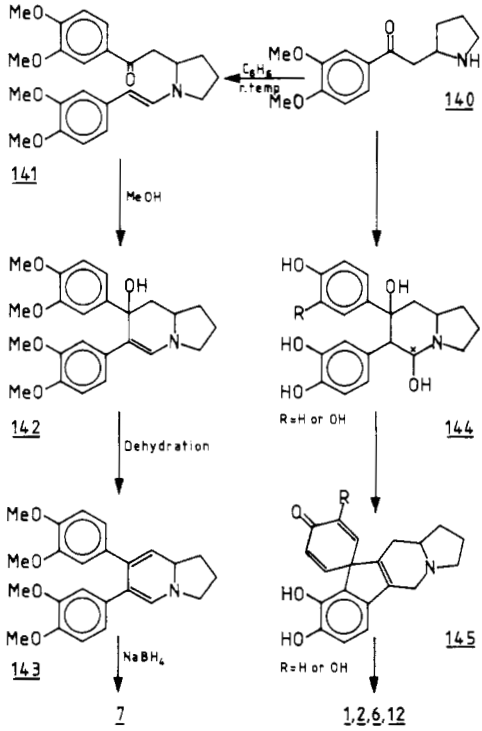
To perform a biogentically patterned synthesis of **7** (80) Δ^1-pyrrolideine (**54**) was reacted with 3,4-dimethoxybenzoyl-acetic acid; the resulting **140**, when condensed with 3,4-dimethoxyphenylacetaldehyde, yielded the enamine **141**. Cyclization to intermediates **142** and **143** was followed by reduction with sodium borohydride to produce racemic **7**.

4. Biosynthesis of the Phenanthroindolizidine Alkaloids

The biosynthesis of the phenanthroindolizidine alkaloids was readily envisaged as occurring from two molecules of phenylalanine and a molecule of ornithine or its equivalent. Initial experiments (81) in *T. asthmatica* indicated that a substituted benzoylacetic acid condensed with Δ^1-pyrrolideine (originating from ornithine) to form analogues of **140**. When reacted



with 3,4-dihydroxyphenylpyruvic acid (originating from 2-^{14}C tyrosine) these analogues yielded compounds similar to **144**. This compound was converted by oxidative coupling to **1** and related alkaloids in which the ^{14}C-label appears in the C-9 position. If the experiment is carried out with 2-^{14}C-labelled phenylalanine (82), then the ^{14}C-label appears in the C-14 position. Benzoic acid 1-^{14}C was not incorporated into **1**, while sodium acetate-2-^{14}C was efficiently incorporated, but the location of ^{14}C in **1** was not determined. The results indicated that phenylalanine is the precursor of the "upper" benzene ring and C-14 of the molecule, while



tyrosine was incorporated into only the "lower" benzene ring and C-9. This is not entirely surprising as similar results were obtained earlier with lycorine alkaloids (83,84). It was shown later (85–87) that ^{14}C or ^{3}H labelled phenacylpyrrolidine derivatives, e.g. **140**, are incorporated into **2** and can be regarded as precursors of compounds similar to **7**, which can cyclize through an intermediate of the type **145** to **1**, **2**, **6**, **12**, etc. These findings were confirmed (88) when cinnamic acid-2-^{14}C was incorporated efficiently into the predicted positions of the phenanthroindolizidine ring system.

5. Biological activity of the phenanthroindolizidine alkaloids

That extracts from *Tylophora* and related species are pharmacologically active was initially recorded in the Bengal Pharmacopoeia (89), the Pharmacopoeia of India (11,13), and in the Philippines (27). Other publications (14,24) mention especially the emetic and vesicant properties. In this century more detailed examinations of the biological activity (15,16,90), especially that of tylophorine and the *Tylophora* alkaloids, established their influence on the respiratory and circulatory systems and their depressant effect on the heart muscles. The effective use of *T. asthmatica* leaves in the treatment of allergic disorders, especially of asthma, was confirmed (91,92). Leaf and stem extracts (91) of *T. indica* and the alkaloids **12** (93,94) and **6** (19) showed antileukemic activity. Antofine (**18**), possesses pronounced antifungal and antibacterial activity (34).

THE SIMPLE INDOLIZIDINE ALKALOIDS

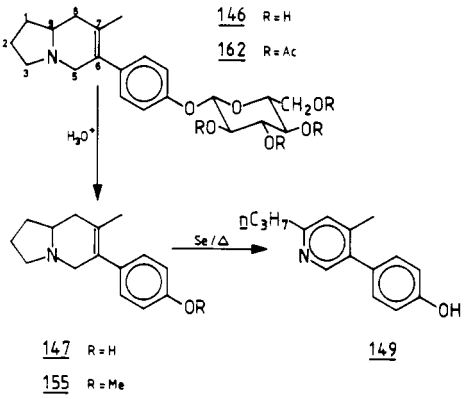
A. *The Convolvulaceae family*

1. Isolation of the alkaloids

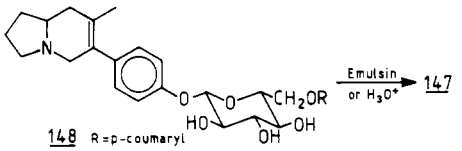
This plant family is well known for plants (Argyreia, Ipomoea, Rivea, Turbina) which contain hallucinogenic alkaloids of the ergoline type and have been used for divinatory purposes in Mexico since the time of the Aztecs (96–101). The presence of indolizidine alkaloids in *Ipomoea alba* L. was first reported by Gourley *et al.* (102), who isolated (+)-ipalbine (**146**), $C_{21}H_{29}NO_6$, (+)-ipalbidine (**147**), $C_{15}H_{19}NO$, and a minor unidentified alkaloid. Later Dawudar *et al.* (103) isolated ipomine (**148**), $C_{30}H_{35}NO_8$, and ipalbidine from *I. muricata* Jacq.

2. Structure elucidation of the alkaloids

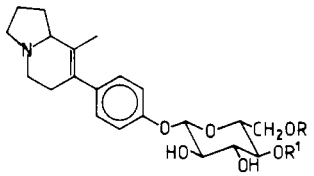
Ipalbine (**146**) *and Ipalbidine* (**147**).—Hydrolysis of **146** with dilute acid gave D-glucose and ipalbidine (**147**), indicating that ipalbine is β-D-glucosylipalbidine. Ipalbidine (**147**) contains a tertiary nitrogen, a C-methyl group and a phenolic hydroxyl group (uv evidence) to which the glucoside is attached in **146**. The presence of an ethylenic double bond was shown by forming the oily dihydroipalbidine, $C_{15}H_{21}NO$, on hydrogenation in acetic acid over Pd/C catalyst. The presence of a phenyl group among the rings it contains was established by showing that a total of four double bonds could be hydrogenated in acetic acid over PtO_2. Selenium dehydrogenation of **147** gave 5-*p*-hydroxyphenyl-4-methyl-2-*n*-propylpyridine (**149**). Consideration of the data obtained from uv, nmr, and mass spectra established the structures of the alkaloids as **146** and **147** (102).



Ipomine (**148**).—Acid hydrolysis of **148** gave **147**, D-glucose and *p*-coumaric acid. As enzymatic hydrolysis with emulsin also yielded **147**, glucose is attached to the molecule by a β-linkage. That C-1 of D-glucose is attached to the phenolic hydroxy group of **147** (and not to *p*-coumaric acid) was shown by methylation of **148** with dimethylsulfate in the presence of potassium carbonate followed by acid hydrolysis of the methylated product. Allegedly 2,3,6-tri-*O*-methyl-D-glucopyranose was obtained, showing that the carboxyl group of the *p*-coumaric acid is linked to the C-4 hydroxyl group of the D-glucose portion of the molecule. Structure **150**, originally assigned to ipomine, was changed to **151** on the basis of ^{13}C nmr evidence which indicated that the linkage of *p*-coumaric acid is at C-6 (104). The structure of ipomine is, however, incorrectly represented by both of the above formulae. It should be **148** as the ipalbidine portion of ipomine is misprinted in both papers (105).



148 R=p-coumaryl

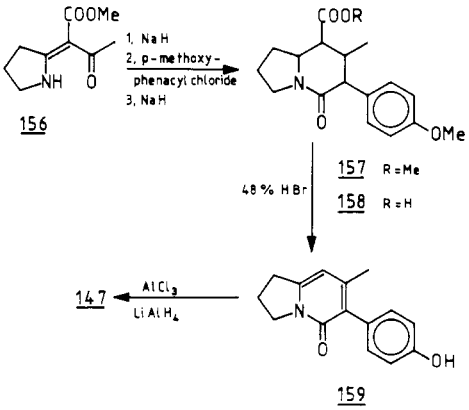


150 R=H; R^1=p-coumaryl

151 R=p-coumaryl; R^1=H

3. SYNTHESIS OF THE ALKALOIDS

Ipalbidine (**147**).—The synthesis of racemic **147** (106) was accomplished by one of the methods employed for the synthesis of septicine (7) (78). The hydroxymethylene derivative of ethyl 4-methoxyphenylacetate was reduced by sodium borohydride to the hydroxy-ester and converted to its chloride which gave **152** on condensation with ethyl 2-pyrrolidinyl acetate (107,108). Dieckmann condensation of **152** (R=H), followed by hydrolysis and decarboxylation, yielded the indolizidone **153** (R=H), which was reduced to the carbinol **154** by methyl lithium. Dehydration of **154** with H_2SO_4 gave *O*-methyl ipalbidine (**155**), which was demethylated to (±)-**147** by aluminium chloride. The racemate of **147** was also synthesized (109) as follows. Condensation of 2-methoxy-1-pyrroline, prepared from 2-pyrrolidone by methylation with dimethyl sulfate, with methyl acetoacetate at 85° without solvent gave the ketoester **156**, the sodium salt of which reacted with *p*-methoxyphenacyl chloride to give a nonisolable intermediate which cyclized to **157** (R=Me) on heating with further amounts of sodium hydride. Simultaneous hydrolysis of some of the ester gave the acid **158** (R=H). Hot 48% hydrobromic acid decarboxylated and demethylated **158** to the pyridone derivative **159**, which was reduced with excess aluminium chloride and lithium aluminium hydride in tetrahydrofuran to (±)-**147**. Finally (±)-**147** was also synthesized by Stevens *et al.* (79) using the route employed for the synthesis of **7**, which follows the same sequence of reactions as the synthesis described above, *i.e.*, from **160** (R=H) to **147** through **161**, **153** and **154**.

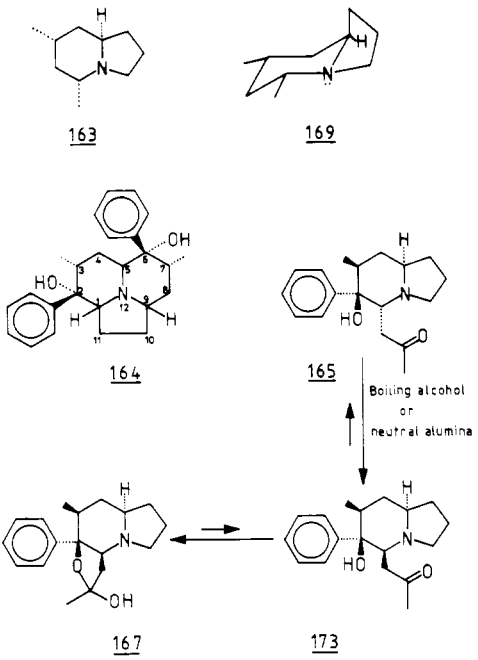


Resolution of the racemate was achieved by fractional crystallization of either the (+)- or the (−)-di-*O*-*p*-toluolyl tartaric acid salts of the *O*-acetate of **147**. Hydrolysis with dilute sodium hydroxide of the enantiomeric acetates gave (+)- and (−)-**147**, respectively. Both bases were recovered and purified by high vacuum distillation.

Ipalbine (**146**).—Tetraacetyl-α-D-bromoglucoside gave with (+)-**147** in acetone in presence of dil. sodium hydroxide the (+)-tetra-*O*-acetylipalbine (**162**) in low yield (109). This material deacetylated readily with a catalytic amount of sodium methoxide in dry methanol to (+)-**146**.

4. BIOSYNTHESIS OF THE ALKALOIDS

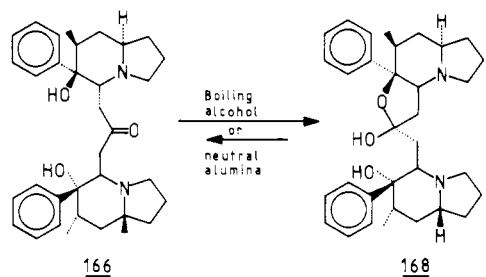
The fact that the mixture of diastereoisomeric glucosides obtained from (±)-**147** is crystalline suggested to the authors (109) that racemic **147** is the biogenetic precursor of **146** as partial selectivity by the plant in the formation of the β-glucosides from (+)- and (−)-**147** would require the formation of a mixture of diastereoisomers in unequal amounts.



B. *The Orchidaceae family*

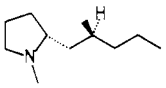
1. ISOLATION OF THE ALKALOIDS

The presence of alkaloids in plants belonging to genera of the Orchidaceae family (110) was reported in 1931. An investigation (111) of 525 species of 129 genera found 77 species which contain appreciable amounts (>0.01%) of alkaloids. Of these, only species of the *Dendrobium* genus produce indolizidine alkaloids. Dendroprimine (**163**) was isolated (112) from *D. primulinum* Lindl. *D. crepidatum* Lindl. (113,114) yielded five alkaloids: crepidine (**164**), crepidamine (**165**), dendrocrepine (**166**), isocrepidamine (**167**), and isodendrocrepine (**168**). The last two are now believed to be artifacts. Another alkaloid, phalaenopsine, was isolated (115) from *Phalaenopsis amabilis* Bl., but it is not yet known whether it really belongs to the indolizidine alkaloids.



2. STRUCTURE ELUCIDATION OF THE ALKALOIDS

Dendroprimine (**163**).—Dendroprimine has the molecular formula $C_{10}H_{19}N$ and contains two C-methyl groups, but no N-methyl groups, double bonds or active hydrogens. Therefore, it must contain two rings and a tertiary nitrogen atom (112). Spectroscopic evidence (ir and nmr) indicated that the two methyl groups were attached to two different tertiary carbon atoms, consequently the nitrogen atom must be at the bridgehead of the ring system. Since dendroprimine methiodide displayed only one *N*-methyl group in the nmr spectrum its structure can be postulated as a dimethylindolizidine. Selenium dehydrogenation of dendroprimine gave 2,4-dimethyl-6- propylpyridine (identified spectroscopically) which established structure **163**, but without the stereochemistry shown. Spectroscopic comparison of the four synthetic racemates (116) of **163** elucidated the structure as either **169** or its mirror image. Finally, dendroprimine was converted (117), by Hofmann degradation of its methiodide followed by hydrogenation, to **170**. As the sign of the CD curve of **170** is opposite to that of *R*(−)-1,2-dimethylpyrrolidine (118), which is derived from *S*(−)-proline, it must have the *R*-configuration at the 2-position of the pyrrolidine ring. Repeated Hofmann degradation of the methohydroxide of **170**, followed by hydrogenation, gave *S*(+)-4-methylnonane (**171**). This was shown to have the same configuration as (+)-methylhexane (119), the absolute configuration of which has already been correlated with (−)-shikimic acid of known absolute configuration. Con-



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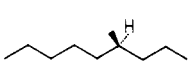

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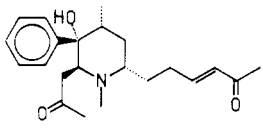

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sequently **171** has the *S* configuration and **163** can be formulated as (5*R*,7*S*,9*R*)-5,7-dimethylindolizidine.

(−)-Crepidine (**164**).—Crepidine has the molecular formula $C_{21}H_{29}NO_3$, and its ir spectrum indicated the presence in the molecule of a hydroxy group bonded to a carbonyl and another hydroxy group bonded intramolecularly to the nitrogen atom (113,114). Hofmann degradation of crepidine methiodide gave an optically active viscous oil **172**, the structure of which was determined by nmr and ms spectroscopy. The full structure of crepidine was elucidated by X-ray diffraction studies of its methiodide as **164** (113, 120).

(±)-*Crepidamine* (**165**).—Crepidamine has the molecular formula $C_{15}H_{25}NO_2$, and its nmr spectrum is similar to that of **172** except for signals due to the *N*-methyl group and the α,β-unsaturated ketone system (114). Its ir spectrum indicates the presence of an intramolecular OH . . . N bonding. The fact that the two rings of the indolizidine system are *trans* to each other is supported by weak Bohlmann bands at 2720 and 2820 cm^{-1} (121,122).

(±)-*Dendrocrepine* (**166**).—Dendrocrepine has the molecular formula $C_{33}H_{44}N_2O_3$, and its nmr spectrum is similar to that of **165**. The structure **166** was elucidated by X-ray diffraction of its hydrobromide (123), while the steric inhibition of the rotation of the phenyl groups in the molecule was investigated by ^{13}C-nmr spectroscopy (124).

Isocrepidamine (**167**).—Isocrepidamine (114) was formed by ready racemization of **165** either in boiling alcohol or by chromatography on neutral alumina, a reaction of β-aminoketones known to occur with pyrrolidine and piperidine alkaloids (125,126) by ring-opening and reclosing reactions. In the case of isocrepidamine, however, the initially formed thermodynamically less stable hydroxyketone **173** cyclized to the corresponding hemiketal **167**.

(±)-*Isodendrocrepine* (**168**).—Isodendrocrepine (113) was formed by ready racemization of dendrocrepine (**166**), in the same way **165** was converted to **167**. As reduction of isodendrocrepine with lithium aluminium hydride gave only two dihydro compounds, this reaction involves only one center in the molecule. Consequently isodendrocrepine is represented by **168**.

INDOLIZIDINE ALKALOIDS FROM FUNGAL AND ANIMAL SOURCES

A. *Alkaloids of Rhizoctonia leguminicola*

1. Isolation and structure of slaframine (**175**)

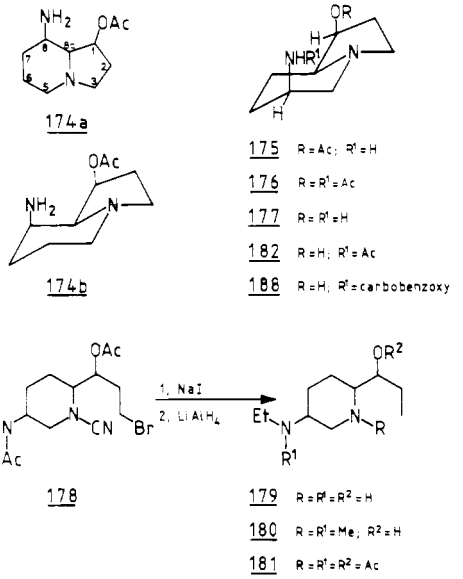
The excessive salivation of ruminants fed on red clover hay was shown to be due to alkaloids produced by *R. leguminicola* (127,128). The initially isolated amorphous alkaloid (129) was later crystallized, named slaframine (130), and assigned the molecular formula $C_{10}H_{18}N_2O_2$.

The erroneous structures **174a** and **174b**, the latter of which depicts its proposed stereochemistry, were later modified (131) to **175** on the basis of spin decoupling results in the nmr spectrum of *N*-acetylslaframine (**176**) obtained from the base on acetylation with acetic anhydride and by comparison of its nmr spectrum with that of the corresponding isomeric 1-hydroxyindolizidine of known stereochemistry. Slaframine yields, on boiling with 1N sodium hydroxide desacetylslaframine, (**177**), $C_{15}H_{16}N_2O$, which, together with spectroscopic evidence, indicates the presence of one primary and one tertiary amino- and one acetylated secondary hydroxyl groups. Reaction of *N*-acetylslaframine with cyanogen bromide yields the ring-opened cyanamino bromide, $C_{13}H_{20}N_3O_3Br$, (**178**), which gives, on treatment with sodium iodide followed by lithium aluminium hydride reduction, **179**, $C_{10}H_{22}N_2O$. Methylation with formaldehyde and formic acid gives **180**, $C_{12}H_{26}N_2O$, while acetylation with acetic anhydride yields **181**, $C_{16}H_{28}N_2O_4$.

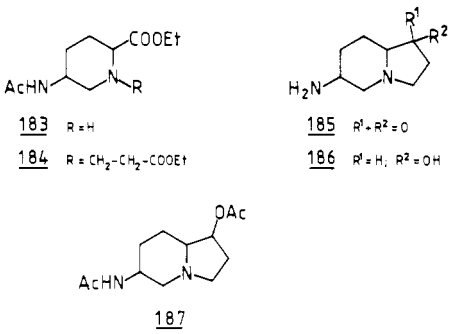
The absolute configuration (132) at C-1 was determined by Horeau's method (133,134), *i.e.*, by treatment of *N*-acetyl-*O*-desacetylslaframine (**182**) with α-phenylbutyric anhydride. This gave residual (−)-α-phenylbutyric acid, thus establishing *S*-configuration at C-1. This result confirmed the conclusion reached earlier by another research group *via* similar reasoning (135).

2. Synthesis

Conversion (136) of 2-bromo-5-nitropyridine (137) *via* the corresponding nitrile into 5-acetamido-2-carbethoxypyridine (138) followed by catalytic hydrogenation at 50 psi (139) gave ethyl 5-acetamidopipecolate (**183**), which reacted with ethyl acrylate (140) on heating in ethanol for two days to give **184**. Dieckmann cyclization with potassium *t*-butoxide in toluene



at 0° gave a diester which, when hydrolyzed and decarboxylated by boiling with 8N hydrochloric acid for 5.5 hrs, afforded **185**. Sodium borohydride reduced **185** to a mixture of stereoisomeric alcohols **186**, which was acetylated to another mixture of four stereoisomeric 1-acetoxy-6-acetamidoindolizidines **187**. This mixture of indolizidines was separated by careful chromatography on alumina and one of these, the *cis*, *cis*-1-acetoxy-6-acetamidoindolizidine, was proved to be identical with authentic (±)-**176** by spectroscopic and chromatographic comparisons of the two compounds. Deacetylation of the synthetic (±)-**176** by prolonged

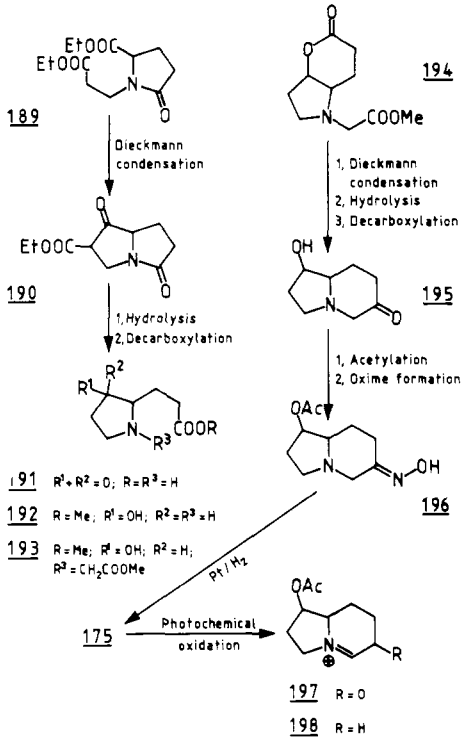


boiling with hydrazine hydrate gave synthetic **177**, which could be converted into its *N*-carbobenzoxy derivative **188**. Acetylation, followed by removal of the protective group by hydrolysis with hydrobromic acid in acetic acid, yielded synthetic (±)-**175**, identical with the natural alkaloid.

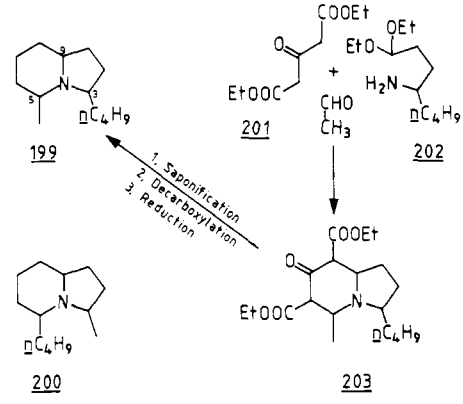
A stereoselective synthesis (141) of slaframine has also been described. Condensation of *L*-(+)-glutamic acid with acrylonitrile followed by esterification of the product furnished ethyl *N*-(β-ethoxycarbonylethyl)-5-oxopyrrolidine-2-carboxylate (**189**). Dieckmann condensation with sodium ethoxide produced the racemic pyrrolizidine derivative **190**. Hydrolysis and decarboxylation of **190** occurred with simultaneous amide ring opening to **191**, which was hydrogenated over PtO_2 in methanol to form the corresponding alcohol methyl ester **192**. Alkylation of **192** with methyl bromoacetate generated a mixture of **193** and **194** (the latter is convertible to **193** by methanolysis). Dieckmann condensation of the above mixture gave an unstable product which was hydrolyzed and decarboxylated to **195**. Acetylation of **195**, followed by oxime formation produced a separable mixture of the *syn*- and *anti*- forms of **196**, which were hydrogenated to synthetic **175**. Assuming that both catalytic hydrogenation processes used during this synthesis add the hydrogens to the double bonds from the less hindered side of the molecule, the relative configuration of the product obtained this way should be identical with that of **175** obtained from natural sources. The nmr spectra of the intermediates are consistent with this formulation.

3. Biological activity

The parasympathomimetic action (127,128,142) of the salivation factor, slaframine, resembles that of acetylcholine. The active component (**197**) formed by rat or porcine liver

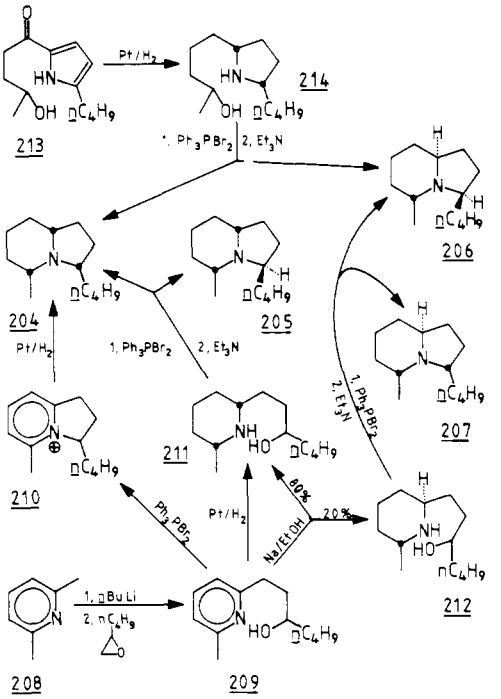


microsomal oxidation is accompanied by a non-active compound (**198**) from which it can be separated by ion-exchange chromatography. Photochemical oxidation of **175** produced the same two compounds, of which **198** is inactive, while the structure of the active one is represented by **197**.



B. *Alkaloids of the Pharaoh Ant*

The pharaoh ant (143) which infests heated buildings such as bakeries and hospitals (144,145) and carries pathogenic bacteria possesses three alkaloidal pheromones. These were extracted from the worker ants and identified with the help of gas chromatography, ir, nmr and ms as pyrrolidines and an indolizidine derivative. The latter has the molecular formula $C_{13}H_{25}N$, and a methyl and a butyl substituent in positions 3- and 5- of the ring system, i.e. **199** or **200**. Synthesis of a mixture of the stereoisomers of **199** was achieved by condensation of diethyl 3-oxoglutarate (**201**) with 4-aminooctanal diethylacetal (**202**) and acetaldehyde to 3-butyl-5-methyl-6,8-dicarboxyethyl-7-oxoindolizidine (**203**), which was saponified, decarboxylated and reduced to an isomeric mixture of 3-butyl-5-methylindolizidines (**199**). One of the isomers in the mixture was then shown by bioassay to be identical with the natural pheromone. As the alkaloid contains three asymmetric carbon atoms, it can be represented by four stereoisomeric structures, **204**, **205**, **206** and **207**. In order to establish which one represents the correct stereochemistry of the alkaloid, all four structures were synthesized unambiguously (146,147).



Reaction of 2,6-lutidine (**208**) with *n*-butyl lithium followed by 1,2-epoxyhexane gave **209**, which cyclized to **210** on treatment with triphenylphosphine dibromide. Hydrogenation of **209** over platinum oxide gave the *cis*-piperidyl alcohol **211**, while reduction with sodium in alcohol produced a 4:1 mixture of **211**, and the corresponding *trans*-isomer **212**. Cyclization of **211** with triphenylphosphine dibromide followed by reaction with triethylamine produced a mixture of **204** and **205**, while cyclization of **212** yielded, under the same conditions, **206** and **207**. The compound represented by **204** could be identified in the first mixture as it was known from an earlier alternative synthesis. The compound represented by **206** could be identified in the latter mixture as it could be synthesized *via* the following alternative route. The pyrrole derivative **213** was hydrogenated over platinum oxide to give the *cis*-pyrrolidine derivative **214**, which gave rise to a mixture of the known **204** and **206** on cyclization with triphenylphosphine dibromide followed by reaction with triethylamine.

The conformation of the four stereoisomers **204**, **205**, **205**, and **207** was studied (121) with the help of nmr data and by investigation of the Bohlmann band intensities (122) in their ir spectra since the applicability of these criteria to indolizidines has already been demonstrated (148). The spectral data confirm the assignments made and suggest that in the all *cis*-**204** the piperidine ring is in the boat conformation to relieve the steric crowding of the substituents located on C-3 and C-5. This forces the methyl group into the axial position.

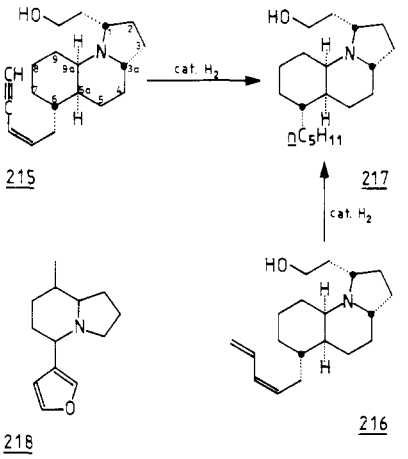
Ritter *et al.* (149), who named the active component of *Monomorium pharaonis* monomorine-I, assigned to it the all *cis*-**204** configuration. In addition to monomorine-I, another indolizidine derivative, monomorine-VI, was also isolated. This is claimed to be the 3-hexenyl analogue of monomorine-I. The pharaoh ant queen produces other pheromones as well, and the amount and the ratio of the monomorines vary considerably between extracts obtained from workers and queens.

C. *Alkaloids of the Dendrobatidae*

Members of this neotropical frog family produce numerous nitrogenous skin toxins (150–152) such as steroidal, decahydroquinoline and spiroalkaloids, but only *Dendrobates histrionicus* (153–155) is known to contain indolizidine alkaloids as well (156). Two indolizidine alkaloids were isolated: gephyrotoxin (**215**), formerly known as HTX-D (157), and dihydrogephyrotoxin (**216**) (158). The new name originating from the Greek, "gephyra" meaning "bridge", is a very appropriate one as these two alkaloids bridge the two main groups of alkaloids of the dendrobatid alkaloids, *viz.*, the decahydroquinolines (the pumiliotoxin class) and those with a vinylacetylene side chain (the histrionicotoxin class).

Gephyrotoxin has the molecular formula $C_{19}H_{29}NO$. It has an alcoholic hydroxyl group, which can be acetylated and *p*-bromobenzoylated and contains a vinylacetylenic side chain. Its structure was elucidated with the help of nmr spectroscopy. Gephyrotoxin is hydrogenated to hexahydrogephyrotoxin **217**. X-ray crystallographic analysis of its hydrobromide (158) established its structure and absolute configuration as [1*S*,3a*S*,5a*S*,6*S*(*Z*),9a*R*,10*R*] dodecahydro-6-(2-penten-4-ynyl)pyrrole[1,2-a]quinoline-1-ethanol (**215**).

Dihydrogephyrotoxin, $C_{19}H_{31}NO$, (**216**), differs from gephyrotoxin only in having a 6-(penta-2,4-dienyl) side chain on C-6 instead of a 6-(penten-4-ynyl) chain. It can be hydrogenated to a tetrahydro derivative which is identical with **217**.



Unlike alkaloids of the histrionicotoxin class, **215** does not possess anticholinergic activity but behaves as a moderately active muscarinic antagonist.

D. *The Alkaloids of the Castor Fiber*

Reinvestigation (159) of the constituents present in the much-sought-after scent glands of the Canadian beaver established the presence, in 0.0002% of partly dried beaver glands, of one indolizidine alkaloid, **218**, together with fourteen other alkaloidal components. They include seven quinolizidine, one tetrahydroisoquinoline, and six pyrazine alkaloids. Only one of the quinolizidine alkaloids, (−)-castoramine, had been isolated earlier (160). The structure, but not the stereochemistry and absolute configuration, of the alkaloid was established with the aid of mass spectroscopy as being 5-(3-furyl)-8-methylindolizidine, **218**.

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