Phenanthroindolizidine and Related Alkaloids: Synthesis of Tylophorine, Septicine, and Deoxytylophorinine †

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Tylophorine (1) is synthesized in two ways. The first method begins with the synthesis of the amide-ester (7), which on reaction, successively, with triethyloxonium fluoroborate and sodium borohydride, gives the amino-ester (8) selectively; hydrolysis and polyphosphoric acid-catalysed ring-closure of compound (9) gives the ketone (10) which yields tylophorine (1) on Clemmensen reduction. An alternative approach is by a biogenetically patterned sequence which involves condensation of (3,4-dimethoxybenzoyl)acetic acid (26) with 1-pyrroline (24) generated either *in situ* from putrescine by pea-seedling diamine oxidase or from ornithine by oxidation with *N*-bromosuccinimide; the product (16) condenses with 3,4-dimethoxyphenylacetaldehyde in benzene to give an enamine [as (12)]. This undergoes cyclisation and dehydration in methanol; sodium borohydride reduction then gives the alkaloid septicine (19) which, on oxidation with thallium(III) trifluoroacetate, yields tylophorine (1). Deoxytylophorinine (34) is made in an exactly analogous manner to the latter method for tylophorine.

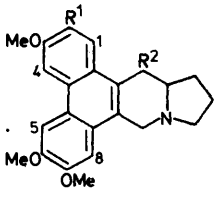
TYLOPHORINE (1), which is one of the major alkaloids of *Tylophora asthmatica* Wight *et* Arn. and is also found in other species,[1] has been the subject of several syntheses.[1,2] An interest in the biosynthesis of the unusual phenanthroindolizidine skeleton exemplified in tylophorine (1) has prompted us to develop two syntheses of this alkaloid. The second of these is based on a consideration of the likely biosynthesis of phenanthroindolizidine alkaloids (*cf.* ref. 3).

Our first synthesis involved the construction of the phenanthrene (9) as a key intermediate. Photolysis of the methyl ester of 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)cinnamic acid (3),[4] in the presence of air and iodine, gave methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate (5)[5] as the major product. Whilst this photolytic reaction does not proceed in outstanding yield it has the advantage over the comparable Pschorr reaction[5,6] in giving a much improved yield over fewer steps. Hydrolysis of the ester (5) gave the acid (6) which was condensed with methyl prolinate[6] using dicyclohexylcarbodi-imide. The amide (7) was obtained in good yield. It could be prepared more conveniently, and in slightly better overall yield, under conditions similar to those used above, by reaction of the cinnamic acid (3) with methyl prolinate followed by photolytic cyclisation of the product (4).

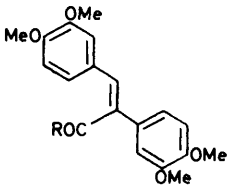
It has been shown that sodium borohydride reduction of the salts formed by *O*-alkylation of secondary and tertiary amides with triethyloxonium fluoroborate gives the corresponding amines.[7] As simple esters are reported to be unreactive towards the latter reagent[8] it seemed likely that the amide-ester (7) could be reduced to the amino-ester (8). In the event, a good yield of the desired product (8) was obtained.

Hydrolysis of the ester (8) to the corresponding amino-acid (9) was achieved under basic but not acidic conditions. Polyphosphoric acid-catalysed cyclisation of this product gave the unstable ketone (10).[9] It was not successfully characterized but the alcohol, obtained by sodium borohydride reduction, gave physical data consistent with the structure (11). The alcohol (11) would not give tylophorine (1) by hydrogenolysis but the ketone (10) was converted into tylophorine (1), albeit in poor yield, by a Clemmensen reduction (*cf.* ref. 9).

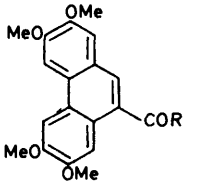
A consideration of the likely biosynthesis of alkaloids such as tylophorine (1) suggested that compounds with structures represented by (16) and (19) were likely to be



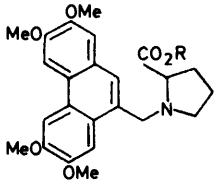
(1) R^1 = OMe, R^2 = H
(2) R^1 = H, R^2 = OH



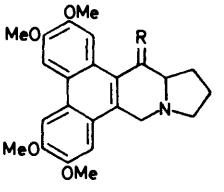
(3) R = OH
(4) R = 2-methoxycarbonylpyrrolidinyl



(5) R = OMe
(6) R = OH
(7) R = 2-methoxycarbonylpyrrolidinyl



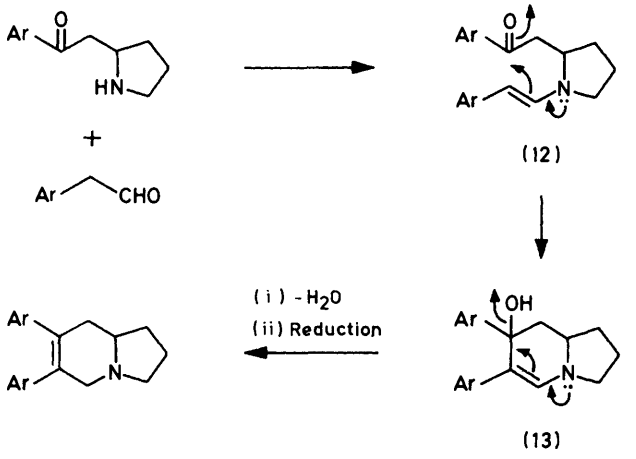
(8) R = Me
(9) R = H



(10) R = O
(11) R = H, OH

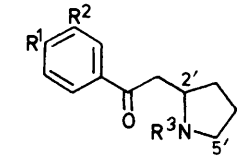
† Part of this work has appeared in preliminary form: C. J. Moody and R. B. Herbert, *Chem. Commun.*, 1970, 121; R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. Chem. Soc., Chem. Commun.*, 1976, 450.

key intermediates. Indeed, compound (19) is the naturally occurring alkaloid, septicine.[10,11] We were interested to see if we could usefully effect the synthesis of septicine (19), and from it tylophorine (1), by mimicking the likely biosynthetic pathway to these alkaloids (see Scheme). In addition, a successful synthesis along these lines would make available compounds which could be tested as biosynthetic precursors.

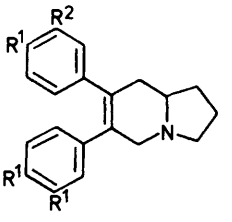


SCHEME

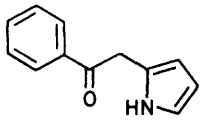
Our first synthetic goal was 2-pyrrolidin-2-ylacetophenone (14). This we sought to synthesize first by hydrogenation of 2-phenacylpyrrole (21) (*cf.* ref. 12) (prepared by condensation of pyrrole with diazoacetophenone [13] in the presence of copper powder); however,



(14) $R^1 = R^2 = R^3 = H$
(15) $R^1 = R^2 = H$, $R^3 = Me$
(16) $R^1 = R^2 = OMe$, $R^3 = H$
(17) $R^1 = OMe$, $R^2 = R^3 = H$



(18) $R^1 = R^2 = H$
(19) $R^1 = R^2 = OMe$
(20) $R^1 = OMe$, $R^2 = H$



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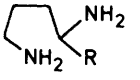


(22) $R = CO_2H$
(23) $R = H$

(24)

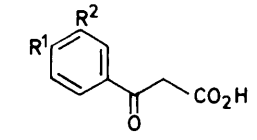
the hydrogenation was unsuccessful under a variety of conditions. An alternative route, which gives compound (14) directly and in good yield, involves the biogenetically modelled condensation of unstable 1-pyrroline (24) (conveniently prepared by reaction of the α-amino-acid, ornithine (22), with *N*-bromosuccinimide [14]) with benzoylacetic acid (25). Eschweiler-Clark methylation of compound (14) gave *N*-methyl-2-phenacylpyrrolidine (15), which was identical with material prepared by another route.[16] Further characterization of compound (14) was through its *N*-benzoyl- and *N*-acetyl-derivatives.

A slightly different route to compound (14) involves the preparation of 1-pyrroline (24) by oxidation of putrescine (23) using pea-seedling diamine oxidase.[17,18] The reaction is carried out in aqueous buffer solution at pH 7 and, apart from the diamine oxidase, the enzyme catalase is present to decompose hydrogen peroxide formed in the putrescine oxidation. Benzoylacetic acid is also present in the reaction mixture and reacts with the 1-pyrroline (24) to give compound (14) in excellent yield. We confirm that this is a very efficient way of making such compounds in high yield (see also the following paper); the preparation of a large number of diamine oxidase units is simple, and partially purified enzyme is entirely satisfactory for synthetic purposes. We have used both methods for the preparation of 3′,4′-dimethoxy-2-pyrrolidin-2-ylacetophenone (16) and have obtained 51 and 85% yields for the sequences beginning with ornithine and putrescine, respectively. It is to be noted that since both putrescine and ornithine are available commercially with a variety of radioactive labels, access to suitably labelled 2-pyrrolidin-2-ylacetophenones for biosynthetic experiments is simply gained either from appropriately labelled putrescine or appropriately labelled ornithine. It may be noted that [5-^{14}C]ornithine is converted into 2-pyrrolidin-2-ylacetophenone which is labelled exclusively at C-5.[19]

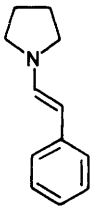
Further consideration of the likely biosynthesis of tylophorine indicated a pathway essentially as outlined in the Scheme. It was hypothesized that reaction would occur between a keto-amine of type (14) and a phenylacetaldehyde derivative (or equivalent α-keto-acid) to give the enamine (12). Reaction of enamines with ketones is fairly uncommon.[20] Reaction here would give compound (13) which on reduction would afford compound (18), a simple analogue of septicine (19). It has been reported [21] that pyrrolidine condenses with phenylacetaldehyde in refluxing benzene with azeotropic removal of water to give compound (28). We found that the condensation occurred rapidly in benzene at room temperature (in the presence of molecular sieve). Under similar mild conditions, 2-pyrrolidin-2-ylacetophenone (14) reacted with phenylacetaldehyde (29) to give the enamine [as (12)]. The two reactants were mixed in hexadeuteriobenzene and examined immediately by n.m.r. spectroscopy; the aldehyde proton had disappeared to be replaced by a signal at δ 5.4, which is assigned to one of the enamine protons. No further reaction occurred in benzene but when the solvent was changed to dry methanol the signal for the enamine proton was absent from an n.m.r. spectrum taken after an hour. It is apparent that under these protic conditions cyclisation and dehydration occurs *via* the enol (13) (or equivalent structure); sodium borohydride reduction of the reaction mixture appropriately gave 6,7-diphenyl-1,2,3,5,8,8a-hexahydroindolizine (18) (30%) with physical data corresponding to those previously

recorded.[22] No other significant products could be detected.

Encouraged by the observation that *N*-styrylpyrrolidine (28) was formed rapidly even in methanol, we investigated whether the reaction of compound (29) with compound (14) to give, ultimately, compound (18), could be carried out in methanol alone: we obtained compound



(25) $R^1 = R^2 = H$
(26) $R^1 = R^2 = OMe$
(27) $R^1 = OMe, R^2 = H$



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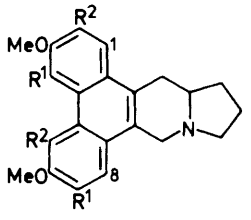
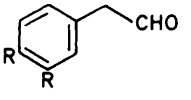
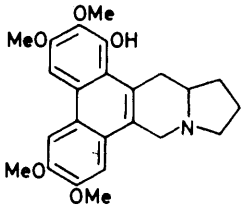


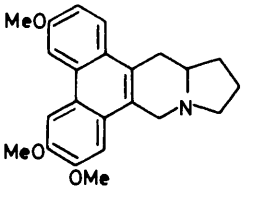
(31) $R^1 = H, R^2 = OMe$
(32) $R^1 = OMe, R^2 = H$



(29) R = H
(30) R = OMe



(33)



(34)

(18), again in 30% yield. Use of sodium cyanoborohydride as a reducing agent under conditions known [23] to favour reduction of immonium salts rather than carbonyl functions did not improve the yield.

Septicine (19) was prepared from 3',4'-dimethoxy-2-pyrrolidin-2-ylacetophenone (16) and 3,4-dimethoxyphenylacetaldehyde (30).[24] The pyrrolidine (16) was synthesized by reaction of 1-pyrroline (*cf.* above) with (3,4-dimethoxybenzoyl)acetic acid (26). This acid was obtained by alkaline hydrolysis of the corresponding ethyl ester, itself prepared by adaptation of a convenient procedure.[25] The condensation of compound (16) with compound (30) was carried out in benzene; cyclisation of the enamine [as (12)] and subsequent dehydration and reduction was in methanol. A 24% yield of (±)-septicine (19) was obtained. The synthetic septicine was identical with the natural material (apart from optical activity).

Thallium(III) trifluoroacetate has found application as an efficient coupling reagent for the synthesis of biaryls.[26,27] We found that one equivalent of this reagent very efficiently converted septicine (19) into tylophorine (1); none of the isomeric, more sterically hindered, alkaloids, *e.g.* tylocrebrine (31), was obtained. When two equivalents of thallium(III) trifluoroacetate were used a different product was obtained. It was clear from its mass and n.m.r. spectra that its structure corresponded to tylophorine plus an extra phenolic hydroxy-group; it gave a methyl ether on treatment with diazomethane. The same phenolic product was obtained from tylophorine (1) on treatment with one equivalent of thallium(III) trifluoroacetate. Comparison of the n.m.r. spectrum of the new product with that of tylophorine (1) showed that the two lowfield protons associated with C-4 and C-5 were still present, although one was shifted due to the presence of the hydroxy-group (δ 7.80 to 7.45). In the n.m.r. spectra of tylophorine (1), tylocrebrine (31),[9] and isotylocrebrine (32) [11] the C-8 proton gives a signal at higher field (δ 7.12—7.25) than the signal for the C-1 proton (δ 7.30—7.77). Since the remaining proton in the new product gave a signal at δ 7.15 we conclude that its structure is (33). A related aromatic acetoxylation with thallium(III) acetate has been observed in the synthesis of isoquinolines.[27]

Tylophorinine (2) is, like tylophorine (1), a major alkaloid of *T. asthmatica*.[1] Deoxytylophorinine (deoxypergularinine) (34) has been isolated from *Pergularia pallida*.[28] It was simply synthesized by adaptation of the route to septicine (19) and tylophorine (1). The key intermediate (17) was easily prepared. Condensation with 3,4-dimethoxyphenylacetaldehyde, dehydration, and subsequent reduction gave the indolizine (20). Interestingly, a three-fold higher yield (62%) was obtained if the reaction was carried out in methanol rather than using titanium(IV) chloride (*cf.* ref. 29) in benzene for the condensation and cyclisation. On the other hand, septicine (19) was obtained in higher yield by using titanium(IV) chloride than by using methanol (29% as against 17%). The indolizine (20) was converted into deoxytylophorinine (34) with thallium(III) trifluoroacetate.

Although the yields of compounds (19), (20), and related compounds prepared by the route illustrated in the Scheme are not outstandingly good, the products, *e.g.* compounds (19) and (20), are the only significant ones to be detected. In spite of the moderate yields obtained generally, the sequence to, *e.g.*, compounds (19) and (20) is short and readily adapted to the preparation of various indolizines and of other alkaloids; [29,30] the overall yield is good. The useful application of the route in the study of the biosynthesis of tylophorine (1) and related alkaloids has been demonstrated.[3]

EXPERIMENTAL

M.p.s were obtained on a hot-stage. N.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R32 unless otherwise noted, and mass spectra were obtained on an AEI MS902

mass spectrometer. Column chromatography was carried out using Kieselgel.[31] Organic extracts were dried with magnesium sulphate. Throughout, ether refers to diethyl ether.

3,4-*Dimethoxy*-α-(3,4-*dimethoxyphenyl*)*cinnamic Acid* (3) (cf. *Ref.* 4).—Veratraldehyde (7.8 g), homoveratric acid (10.0 g), acetic anhydride (20 ml) and triethylamine (10 ml) were heated together at 100 °C for 16 h with the exclusion of moisture. Water was added and, after being set aside for 1 h at room temperature, the mixture was poured into a solution of aqueous potassium carbonate (75 g in 475 ml). This mixture was refluxed until nearly all the gummy material had dissolved. The solution obtained was cooled, extracted twice with ether, and then carefully acidified with concentrated hydrochloric acid. The solid which separated was collected and recrystallized from methanol to give 3,4-*dimethoxy*-α-(3,4-*dimethoxyphenyl*)*cinnamic acid* (3) (12.3 g, 75%), m.p. 217.5—220 °C (lit.,[4] 215—217 °C); $\lambda_{max.}$ (EtOH) (log ε), 237 (4.14), 285 (3.91), and 324 nm (3.77); $\nu_{max.}$ (Nujol) 1 675 cm^{-1}; *m/z* 344 (M^+), 329, and 299 (Found: C, 65.3; H, 5.6. $C_{19}H_{20}O_6$ requires C, 65.3; H, 5.65%). On treatment with ethereal diazomethane, the acid (3) gave a *methyl ester* (77%), m.p. 125—126 °C (from cyclohexane); $\nu_{max.}$ (Nujol) 1 712 cm^{-1}; δ($CDCl_3$, 60 MHz) 3.5 (3 H, s), 3.80, 3.82, and 3.84 (3 × 3 H, each s), 3.9 (3 H, s), 7.04—6.55 (6 H, unresolved), and 7.8 (1 H, s) (Found: C, 66.9, H, 6.15. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.14%).

Methyl 2,3,6,7-*Tetramethoxyphenanthrene*-9-*carboxylate* (5).—Methyl 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)-cinnamate (300 mg) and iodine (10.5 mg, 5 mol %) in Spectrosol cyclohexane (430 ml) were irradiated with a Hanovia U.V.S. 500 A quartz lamp; the apparatus was water cooled and the reaction mixture was agitated by a stream of air. By u.v. analysis the reaction was judged to be complete after 35 min. The solvent was evaporated and the residue subjected to column chromatography. After initial elution with benzene–ether, elution with ethyl acetate gave methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate (30%), m.p. 202—204 °C (lit.,[5] 195 °C); $\lambda_{max.}$ (EtOH) (log ε) 226 (4.02), 264 (4.74), 281 (4.44), 290 (4.49), and 327 nm (40.5); $\nu_{max.}$ (Nujol) 1 720 cm^{-1}; δ($CDCl_3$, 60 MHz) 2.93 (3 H, s), 2.95 (3 H, s), 3.02 (9 H, s), 6.04 (1 H, s), 6.46 (1 H, s), 6.52 (1 H, s), 7.19 (1 H, s), and 7.52 (1 H, s) (Found: C, 67.5; H, 5.7. Calc. for $C_{20}H_{20}O_6$: C, 67.4; H, 5.6%). The same ester was obtained from 2,3,6,7-tetramethoxyphenanthrene-9-carboxylic acid (6) (see below) on treatment with methanol and hydrogen chloride under prolonged reflux. The ester was hydrolysed to the acid (6) on refluxing for 3 h with 10% aqueous sodium hydroxide. The acid (6) was identical with the authentic material.[5]

Methyl N-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylcarbonyl*)-*pyrrolidine*-2-*carboxylate* (7) [*from Compound* (6)].—2,3,6,7-Tetramethoxyphenanthrene-9-carboxylic acid (6) (40 mg) was stirred with dicyclohexylcarbodi-imide (26.8 mg) in dichloromethane (2 ml) at 0 °C. Methyl L-prolinate[6] (*ca.* 17 mg) in dichloromethane (2 ml) was added. After the mixture had been stirred at room temperature for 3.5 h, a few drops of glacial acetic acid were added to it, and it was then washed with aqueous sodium hydrogen carbonate and filtered. The filtrate was washed with water, dried, and evaporated. Column chromatography (ether–benzene, chloroform, and 5% methanol in chloroform) gave *methyl* N-(2,3,6,7-*tetramethoxy*-9-*phenanthrylcarbonyl*)*pyrrolidine*-2-*carboxylate* (7) (40 mg, 76%) as a solid. It could be recrystallized from benzene–cyclohexane, m.p. 203 °C; $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 635 cm^{-1}; $\lambda_{max.}$ (EtOH) 260, 286, 305, 314, 341, and 357 nm; *m/z* 453 (M^+) and 325 ($M^+ - C_6H_{10}NO_2$, *m** 233) (Found: C, 65.8; H, 5.85; N, 3.45%; M^+, 453.179 16. $C_{25}H_{27}NO_7$ requires C, 66.2; H, 5.96; N, 3.09%; *M*, 453.178 74).

Methyl N-[3,4-*Dimethoxy*-α-(3,4-*dimethoxyphenyl*)*cinnamyl*]*pyrrolidine*-2-*carboxylate* (4).—To a mixture of methyl L-prolinate (*ca.* 226 mg) and dicyclohexylcarbodi-imide (378 mg) in dichloromethane (10 ml) was added, with stirring, 3,4-dimethoxy-α-(3,4-dimethoxyphenyl)cinnamic acid (550 mg). The mixture was stirred for 18 h at room temperature. The product *methyl* N-[3,4-*dimethoxy*-α-(3,4-*dimethoxyphenyl*)*cinnamyl*]*pyrrolidine*-2-*carboxylate* (4) was isolated as described for compound (7) immediately above. The pure compound (4) (600 mg, 82%) was obtained by column chromatography using chloroform as the eluant. It could be crystallized as a yellow gummy solid from cyclohexane, m.p. 42—46 °C; $\lambda_{max.}$ (EtOH) (log ε) 207 (4.40) and 320 nm (4.15); $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 635 cm^{-1}; *m/z* 455.195 73 (M^+)($C_{25}H_{29}NO_7$ requires *M*, 455.194 40), 327 ($M^+ - C_6H_{10}NO_2$, *m** 235), 299 (*m** 273.5), and 278; δ ($CDCl_3$, 60 MHz) 1.55—2.32 (6 H, unresolved), 3.58 (3 H, s), 3.78, 3.85, and 3.89 (12 H, visible as 3 singlets), 4.45 (1 H, broad), and 6.60—6.96 (7 H, unresolved).

Methyl N-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylcarbonyl*)-*pyrrolidine*-2-*carboxylate* (7) [*from Compound* (4)].—A mixture of methyl *N*-[3,4-dimethoxy-α-(3,4-dimethoxyphenyl)-cinnamyl]pyrrolidine-2-carboxylate (300 mg) and iodine in Spectrosol cyclohexane (300 ml) was irradiated in a quartz flask in three equal portions for 2 h each using a Hanovia U.V.S. 220 arc lamp. Evaporation of the solvent and column chromatography of the residue [ether–benzene (1 : 1) through to ether–chloroform (1 : 1)] gave the amide (7) (27%) identical with material prepared by the alternative route (above).

Methyl N-(2,3,6,7-*Tetramethoxy*-9-*phenanthrylmethyl*)-*pyrrolidine*-2-*carboxylate* (8) *and the Corresponding Acid* (9).—Methyl *N*-(2,3,6,7-tetramethoxy-9-phenanthrylcarbonyl)pyrrolidine-2-carboxylate (400 mg, 0.87 mmol) in dry dichloromethane (12 ml) was added in one portion to triethyloxonium fluoroborate (200 mg, 1.05 mmol). The mixture was stirred for 20 h at room temperature with the exclusion of moisture. The dichloromethane was removed under reduced pressure and absolute alcohol (16 ml) was added. The mixture was stirred at 0 °C and sodium borohydride (93 mg) was added. A yellow suspension formed. The mixture was stirred overnight at room temperature and then poured into water (130 ml). Extraction several times with chloroform gave an oil which was crystallized from benzene–cyclohexane to give *methyl* N-(2,3,6,7-*tetramethoxy*-9-*phenanthrylmethyl*)*pyrrolidine*-2-*carboxylate* (8) (297 mg, 76%), m.p. 160—163 °C; $\lambda_{max.}$ (EtOH) (log ε) 221 (4.32), 258 (4.91), 287 (4.49), 302 (4.26), 339 (3.4), and 353 nm (3.2); $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1}; *m/z* 439 (M^+), 424, 408, and 380; δ ($CDCl_3$, 60 MHz) 3.7 (3 H, s), 4.04 (3 H, s), 4.14 (9 H, s), 4.56 (1 H, d, *J* 12 Hz), 7.2 (1 H, s), 7.48 (1 H, s), 7.82 (2 H, s), and 8.2 (1 H, s).

Hydrolysis of the ester (8) (200 mg) with potassium hydroxide (12 g) in water (80 ml) and ethanol (20 ml) at reflux for 5.5 h gave the acid (9) (79%), m.p. 203—205 °C (from benzene–petroleum); $\nu_{max.}$ 1 710 cm^{-1}; *m/z* 425.184 29 (M^+) ($C_{24}H_{27}NO_6$ requires *M*, 425.183 82), 381, 380, 342, 328, 312, and 311.

2,3,6,7-*Tetramethoxyphenanthro*[9,10-b]*indolizidin*-14-*one* (10).—A mixture of *N*-(2,3,6,7-tetramethoxy-9-phenan-

thrylmethyl)pyrrolidine-2-carboxylic acid (100 mg) and polyphosphoric acid (*ca.* 1 ml) was heated at 104—114 °C under nitrogen and with the exclusion of moisture for 20 min. The mixture was poured into alkaline ice–water. Extraction with chloroform, drying, and evaporation gave 2,3,6,7-tetramethoxyphenanthro[9,10-*b*]indolizidin-14-one (35 mg) which was used immediately for further reactions. Starting material (60 mg) could be recovered from the aqueous solution above on acidification with acetic acid.

2,3,6,7-*Tetramethoxyphenanthro*[9,10-*b*]*indolizidin*-14-*ol* (11).—Crude 2,3,6,7-tetramethoxyphenanthro[9,10-b]indolizidin-14-one (35 mg) was treated with an excess of sodium borohydride in ethanol at room temperature overnight. Usual product isolation gave material which was purified by preparative t.l.c. (20% MeOH in $CHCl_3$) to give two products. The first (10 mg) had $\lambda_{max.}$ (EtOH) 243, 252, 260, 284, 290, 305, 341, and 358 nm; *m/z* 409.188 44 (M^+) ($C_{24}H_{27}NO_5$ requires *M*, 409.188 91), 340.130 95 ($C_{20}H_{20}O_5$ requires *m/z* 340.131 06), 325, 324, 312, and 311. The second compound (2 mg) had a very similar mass spectrum to that of the first compound. It is deduced that these compounds are diastereoisomeric forms of 2,3,6,7-tetramethoxyphenanthro[9,10-*b*]indolizidin-14-ol.

(±)-*Tylophorine* (1) [*from Compound* (10)].—To amalgamated zinc [prepared from zinc wool (2 g) and mercury(II) chloride (0.18 g)] was added 2,3,6,7-tetramethoxyphenanthro[9,10-*b*]indolizidin-14-one (13 mg) in dilute hydrochloric acid (8 ml of concentrated acid in 6 ml of water). The mixture was refluxed for 15 h and then filtered; the solid residue was washed with 2M hydrochloric acid. The combined aqueous solutions were adjusted to pH 8 with aqueous potassium hydroxide and then extracted several times with chloroform. The combined extracts were washed with water, dried, and evaporated to give material which was shown by t.l.c. (20% MeOH in $CHCl_3$) to be a mixture. The material was treated overnight with an excess of ethereal diazomethane; t.l.c. analysis indicated that this had increased the amount of (±)-tylophorine present. Preparative t.l.c. gave pure (±)-tylophorine (2 mg, 16%) which was identical with an authentic specimen (i.r., u.v., and mass spectra).

2-*Phenacylpyrrole* (21).—Diazoacetophenone [13] (6.97 g) was dissolved in dry ether (200 ml). Copper powder (*ca.* 100 mg) and redistilled pyrrole (3.48 g) were added. The mixture was refluxed under nitrogen for 2 h. It was filtered and the solvent was removed under reduced pressure to leave a brown solid residue. The solid was recrystallized [benzene–light petroleum (boiling range 60—80 °C)] to give 2-*phenacylpyrrole* (3.0 g, 32%), m.p. 137—138 °C; $\nu_{max.}$ (Nujol), 3 350, 1 685, 1 605, and 1 590 cm^{-1}; $\lambda_{max.}$ (EtOH) (log ε) 215 (3.89) and 243 nm (4.11); δ($CDCl_3$) 4.30 (2 H, s), 5.90—6.25 (2 H, m), 6.60—6.85 (1 H, m), 7.20—7.67 (3 H, m), and 7.80—8.17 (2 H, m); *m/z* 185 (M^+), 105, 80, and 77 (Found: C, 77.85; H, 5.9; N, 7.25. $C_{12}H_{11}NO$ requires C, 78.00; H, 5.85; N, 7.60%). Attempted hydrogenation for periods of up to 3 d with platinum in acetic acid (1 atm) or trifluoroacetic acid (1 and 2 atm), or with 5% rhodium on alumina (up to 100 atm) in trifluoroacetic acid or acetic acid, failed to give material identifiable as 2-pyrrolidin-2-ylacetophenone (14).

1-*Pyrroline*.—This compound was prepared by modification of the published procedure.[14] DL-Ornithine monohydrochloride (1.67 g) was dissolved in water (20 ml) and the solution was cooled in ice. Bromine liberated during the reaction was driven from the reaction flask by a stream of nitrogen into a solution of 40% aqueous potassium iodide. To the aqueous solution, *N*-bromosuccinimide (1.75 g) was added with stirring during 30 min. Stirring was continued for a further hour with ice cooling. The yellow solution was then warmed on a steam-bath for 5 min to give a colourless solution of 1-pyrroline which was used immediately. The yield (typically 50—60%) was assayed using *o*-aminobenzaldehyde as described.

2-*Pyrrolidin*-2-*ylacetophenone* (14).—Ethyl benzoylacetate (1.1 g) was stirred in 2.5% aqueous potassium hydroxide (50 ml) for 40 h at room temperature. The solution was extracted with ether, then cooled, and acidified with cold 1M sulphuric acid. The precipitate was taken into ether and the aqueous solution was extracted several times with ether. The ether extracts were combined and dried. Evaporation in the cold gave benzoylacetic acid (0.69 g, 74%) which was used immediately.

By carrying out the following reaction at various pH values it was determined that pH 7 is optimal. To a solution of benzoylacetic acid (0.69 g, 3.7 mmol) in methanol (50 ml) was added 1M phosphate buffer (pH 7.25, 4 ml) and a freshly prepared solution of 1-pyrroline (10 ml, 3.0 mmol). The pH was adjusted to 7.0 (1M KOH) and the reaction mixture was stirred under nitrogen for 60 h at room temperature. The brown solution was acidified to Congo Red, cooled, and extracted with ether. The aqueous layer was basified with potassium carbonate and was extracted several times with chloroform, then continuously for 6 h. The combined extracts were dried and the solvent was removed under reduced pressure to leave a brown oil (0.53 g). This was purified by preparative t.l.c. (50% MeOH in $CHCl_3$ plus 1% concentrated aqueous NH_3) to give 2-pyrrolidin-2-ylacetophenone (14) as a colourless oil (0.30 g, 53%) which rapidly went brown in air at room temperature: $\lambda_{max.}$ (EtOH), 211, 234, and 288 nm; $\nu_{max.}$ (film) 3 360, 1 680, 1 605, and 1 585 cm^{-1}; *m/z* 189.114 86 (M^+) ($C_{12}H_{15}NO$ requires *M*, 189.115 38), 120.057 52 (C_8H_8O requires *m/z* 120.056 99; McLafferty rearrangement), 105.034 09 (C_7H_5O requires *m/z* 105.034 04), 84, 77, and 70; δ($CDCl_3$) 1.2—2.1 (4 H, unresolved), 2.8—3.05 (2 H, unresolved), 2.9—3.17 (2 H, m), 3.22 (1 H, s, NH), 3.5 (1 H, m), 7.1—7.6 (3 H, m), and 7.64—8.10 (2 H, m). The pyrrolidine (14) gave an *N*-acetyl derivative (Ac_2O, pyridine, 4 h reflux under N_2) which was distilled in a Kugelröhr (oven temperature 200 °C/0.5 mmHg); $\nu_{max.}$ (film) 1 680, 1 640, 1 600, and 1 585 cm^{-1}, $\lambda_{max.}$ (EtOH) 205 and 246 nm; δ($CDCl_3$) 1.6—2.3 (4 H, m), 2.08 (3 H, s), 2.5—4.2 (5 H, m), 7.4—7.65 (3 H, m), and 7.98—8.2 (2 H, m); *m/z* 231 (M^+), 188, 105, 84, and 77. It also gave an *N*-benzoyl derivative (benzoyl chloride, pyridine, steam-bath for 30 min under nitrogen); $\nu_{max.}$ (film), 1 680 and 1 635 cm^{-1}; *m/z* 293.141 043 (M^+) ($C_{19}H_{19}NO_2$ requires *M*, 293.141 570), 188, 105, 84, and 77.

N-*Methyl*-2-*phenacylpyrrolidine* (15).—To a solution of 2-pyrrolidin-2-ylacetophenone (70 mg) in formic acid (200 mg, 98%) was added formaldehyde (100 mg of a 37—41% aqueous solution). The mixture was heated on a steam-bath for 14 h. Concentrated hydrochloric acid (1 drop) was added and the mixture was evaporated. The residue was dissolved in 2M sulphuric acid and the solution was extracted with ether. It was basified (concentrated aqueous NH_3) and then extracted with chloroform; the extract was dried. Removal of the solvent left *N*-methyl-2-phenacylpyrrolidine as a brown oil (65 mg) which was purified by preparative t.l.c. (50% MeOH in $CHCl_3$ plus 1% concentrated aqueous NH_3) to give the pyrrolidine as a colourless oil (64% yield) which went brown in the air. It was identical by t.l.c. (3

solvents) and n.m.r. and i.r. spectra with authentic material prepared by another route [16] from *N*-methyl-1-pyrroline and benzoylacetic acid.

N-Styrylpyrrolidine.—To a solution of redistilled phenylacetaldehyde (0.8 g, 6.7 mmol) in dry benzene (10 ml) was added freshly distilled pyrrolidine (0.5 g, 7 mmol) and the solution was stirred at room temperature with 4A molecular sieve (0.5 g). At intervals, samples were taken; the solvent was evaporated and the residual oil was dissolved in dry ether for u.v. assay ($\lambda_{max.}$ at *ca.* 305 nm). The optimum reaction time was found to be 30 min. The *N*-styrylpyrrolidine was isolated after 80 min. It was distilled in a Kugelröhr (oven temperature 142—146 °C/0.9 mmHg); $\lambda_{max.}$ 307 and 225 (shoulder) nm; *m/z*, 173.119 58 (M^+) ($C_{12}H_{15}N$ requires *M*, 173.120 44), 172, and 104; δ($CDCl_3$) 1.5—2.18 (4 H, m), 3.0—3.5 (4 H, m), 5.19 (1 H, d, *J* 14 Hz), 7.09 (1 H, d, *J* 14 Hz), and 6.88—7.82 (5 H, m). The product was also obtained in similar yield using dry methanol as solvent.

2-Phenacyl-N-styrylpyrrolidine [*as* (12)].—2-Pyrrolidin-2-ylacetophenone (105 mg, 0.56 mmol) and phenylacetaldehyde (67 mg, 0.56 mmol) were dissolved in dry hexadeuteriobenzene (2 ml). The solution was stirred in the dark. N.m.r. analysis after less than 5 min showed the presence of a doublet at δ 5.4, *J* 14 Hz, assigned to an enamine olefinic proton; no signal due to an aldehyde proton remained. The n.m.r. spectrum was unchanged when examined after a further 2 h. The solvent was removed. The residual oil was identified as *2-phenacyl-N-styrylpyrrolidine*; $\lambda_{max.}$ (ether) 238 and 304 nm; $\nu_{max.}$ (film) 1 685, 1 635, and 1 600 cm^{-1}; *m/z*, 291.161 57 (M^+) ($C_{20}H_{21}NO$ requires *M*, 291.162 31), 275 [structure corresponds to (18)], 206 (reverse Diels–Alder on *m/z* 275), 172, 120 (McLafferty rearrangement), and 105; δ($CDCl_3$) 1.3—5.0 (9 H, unresolved), 5.1 (1 H. d. *J* 14 Hz), and 6.7—8.1 (11 H, m).

6,7-Diphenyl-1,2,3,5,8,8a-hexahydroindolizine (18)—2-Phenacyl-*N*-styrylpyrrolidine was prepared as above (same quantities). It was dissolved in dry methanol (10 ml) and set aside at room temperature for 1 h. Evaporation gave an oil which showed no enamine proton signals in the n.m.r. spectrum. The oil was redissolved in dry methanol and sodium borohydride (50 mg) was added. The mixture was stirred in the dark overnight and then partitioned between water and chloroform. The chloroform layer was dried and evaporated to leave a brown oil which was chromatographed on a column using a solvent elution gradient of chloroform through to 20% methanol in chloroform. 6,7-Diphenyl-1,2,3,5,8,8a-hexahydroindolizine (8) was obtained and further purified by preparative t.l.c. (5% MeOH in $CHCl_3$); yield: 25%.

In an alternative procedure, 2-pyrrolidin-2-ylacetophenone (160 mg, 0.85 mmol) and phenylacetaldehyde (120 mg, 1.0 mmol) were dissolved in dry methanol (10 ml). The mixture was stirred in the dark for 1 h. An excess of sodium borohydride (60 mg) was added and the mixture was stirred for a further 2 h. The indolizine (18) (30%) was isolated and purified as above. It was crystallized from acetonitrile–methanol to give a creamy white solid, m.p. 106–107 °C (lit.,[22] 109 °C), identical by t.l.c. (Me_2CO; 5% MeOH in $CHCl_3$; 20% Et_2O in C_6H_6) and i.r. with authentic material[22] *m/z* 275.167 75 (M^+) ($C_{20}H_{21}N$ requires *M*, 275.167 39), 206.108 82 (reverse Diels–Alder, $C_{16}H_{14}$ requires 206.109 55), and 198 (Found: C, 87.1; H, 7.85; N, 5.05. Calc. for $C_{20}H_{21}N$: C, 87.27; H, 7.64; N, 5.09%).

3,4-Dimethoxybenzoyl Chloride.—To 3,4-Dimethoxybenzoic acid (7.25 g) and oxalyl chloride (4 ml) in dry benzene was added dimethylformamide (1 drop). The mixture was stirred at room temperature until no more gas was evolved (*ca.* 2 h). The solvent was removed to give a solid (7.97 g, 98%) which was used in the next step without purification. A small sample recrystallized from dry benzene had m.p. 69—71 °C (lit.,[32] 69—70 °C); $\nu_{max.}$ (Nujol) 1 768, 1 750, and 1 592 cm^{-1} (Found: C, 53.95; H, 4.35; Cl, 17.9. Calc. for $C_9H_9ClO_3$: C, 54.0; H, 4.5; Cl, 17.8%).

Ethyl 2-(3,4-Dimethoxybenzoyl)acetoacetate (cf. *Ref.* 25).—Sodium wire (0.8 g) was stirred with a solution of ethyl acetoacetate (5.2 g) in dry ether (40 ml) under nitrogen. The suspension of the sodium salt obtained was stirred while a solution of 3,4-dimethoxybenzoyl chloride (3.0 g) in dry ether (40 ml) was added dropwise. The mixture was refluxed for 5 h and set aside overnight. The precipitate was collected, washed with ether, and dried. It was then dissolved in water and the solution was acidified with 10% hydrochloric acid. The resulting oil was extracted into ether which was dried and evaporated to leave ethyl 2-(3,4-dimethoxybenzoyl)acetoacetate as a yellow oil which was used without purification for the next step. The oil crystallized with time and a small sample was recrystallized from ethanol to give a white solid, m.p. 86—88 °C; $\nu_{max.}$ (Nujol) 1 725, 1 713, 1 680, and 1 598 cm^{-1}; *m/z*, 294.109 99 (M^+) ($C_{15}H_{18}O_6$ requires *M*, 294.110 33), 252, 248, 165, and 137; δ($CDCl_3$) 1.27 (3 H, t, *J* 7 Hz), 2.36 (3 H, s), 3.96 (3 H, s), 3.99 (3 H, s), 4.29 (2 H, q, *J* 7 Hz), 5.38 (1 H, s), 6.93 (1 H, d, *J* 9.5 Hz), and 7.52—7.64 (2 H, m) (Found: C, 60.65; H, 6.3. $C_{15}H_{18}O_6$ requires C, 61.0; H, 6.1%).

Ethyl (3,4-Dimethoxybenzoyl)acetate (cf. *Ref.* 25).—A solution of ethyl 2-(3,4-dimethoxybenzoyl)acetoacetate (3.8 g) in 90% ethanol (50 ml) was refluxed with sodium acetate (50 mg) for 6 h and then set aside overnight The solvent was removed under reduced pressure; water (50 ml) was added, and the insoluble brown oil was extracted into ether. The ether extract was dried and evaporated to leave ethyl (3,4-dimethoxybenzoyl)acetate as a brown oil (2.8 g, 86%) which was purified by chromatography ($CHCl_3$). It crystallized with time and could be recrystallized from ethanol, m.p. 41—43 °C, (lit.,[33] 37.5—39.5 °C); $\nu_{max.}$ (film), 1 740 and 1 680 cm^{-1}; *m/z* 252.099 09 (M^+) ($C_{13}H_{16}O_5$ requires *M*, 252.099 77), 222.088 65 ($C_{12}H_{14}O_4$ requires *m/z* 222.089 20), 210.089 65 ($C_{11}H_{14}O_4$ requires *m/z* 210.089 20), and 180.079 56 ($C_{10}H_{12}O_3$ requires *m/z* 180.078 64); δ($CDCl_3$) 1.25 (3 H, t, *J* 8 Hz), 3.93 (2 H, s), 3.94 (6 H, s), 4.21 (2 H, q, *J* 8 Hz), 6.93 (1 H, d, *J* 9 Hz), 7.55 (1 H, broad s), and 7.59 (1 H, d, *J* 9 Hz; further small splitting seen on one arm of signal) (Found: C, 61.95; H, 6.6. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39%).

3′,4′-Dimethoxy-2-pyrrolidin-2-ylacetophenone (16).—(*a*) The synthesis was closely similar to that of 2-pyrrolidin-2-ylacetophenone (14) above. Ethyl (3,4-dimethoxybenzoyl)-acetate was converted into the acid (67%) by alkaline hydrolysis characterized *via* 3,4-dimethoxyacetophenone [$\nu_{max.}$ 1 688 cm^{-1}; *m/z* 180 (M^+) 165, and 137; δ($CDCl_3$) 2.55 (3 H, s), 3.94 (6 H, s), 6.92 (1 H, d, *J* 9 Hz), and 7.55—7.7 (2 H, m)] obtained by heating the acid in concentrated hydrochloric acid for 30 min on a steam-bath. From the (3,4-dimethoxybenzoyl)acetic acid and ornithine was obtained *3′,4′-dimethoxy-2-pyrrolidin-2-ylacetophenone* (16) (0.5 g, 51%); $\nu_{max.}$ (film), 1 695 and 1 668 cm^{-1}; $\lambda_{max.}$ (EtOH), 231, 277, and 305 nm; *m/z*, no M^+, 180 (McLafferty rearrangement), 165, 137, 77, and 70. Compound (16) was unstable and intractable; it was further characterized as its *N*-acetyl derivative (Ac_2O, pyridine, 3 h reflux): $\nu_{max.}$ (film).

1 715, 1 668, 1 645, and 1 590 cm^{-1}; *m/z* 291.148 17 (M^+) ($C_{16}H_{21}NO_4$ requires *M*, 291.147 05), 262 ($C_{14}H_{16}NO_4$ requires *m/z* 262.107 93) 221, 180.078 82 (McLafferty rearrangement; $C_{10}H_{12}O_3$ requires *m/z* 180.078 64), 165.055 67 ($C_9H_9O_3$ requires *m/z* 165.055 16), 137, 126, 111, 83, and 69; δ($CDCl_3$) 1.62—2.18 (4 H, m), 2.09 (3 H, s), 2.28—2.87 (2 H, m), 3.28—3.68 (2 H, m), 3.74 (1 H, m), 3.98 (3 H, s), 4.0 (3 H, s), 7.0 (1 H, d, *J* 8 Hz), 7.7 (1 H, d, *J* 2 Hz), and 7.95 (1 H, dd, *J* 2 and 8 Hz).

(*b*) A solution of (3,4-dimethoxybenzoyl)acetic acid (0.87 g), putrescine (40 ml of a 0.1M aqueous solution), and potassium phosphate buffer (13 ml of a 0.2M aqueous solution, pH 7) was prepared, and adjusted to pH 7. Catalase (0.20 mg) and diamine oxidase (purified to the stage prior to hydroxyapatite chromatography) [18] (3 ml, activity: 6.7 units ml^{-1}) were then added. The solution was incubated on a rotary shaker at 27 °C for 24 h; as the reaction proceeded the solution was occasionally readjusted to pH 7. The solution was acidified with dilute sulphuric acid and was extracted with ether. The aqueous solution was basified with concentrated aqueous ammonia and was extracted thrice with chloroform. The combined extracts were dried and were then evaporated under reduced pressure to give 3′,4′-*dimethoxy*-2-*pyrrolidin*-2-*ylacetophenone* (16) (0.818 g, 85%) as a brown oil which was a single component on t.l.c. (20% MeOH in $CHCl_3$ plus a few drops of concentrated aqueous NH_3); δ($CDCl_3$) 1.1—2.2 (4 H, unresolved), 2.35 (1 H, broad s, exchanged with D_2O), 2.7—3.2 (2 H, unresolved), 3.11 (2 H, d, *J* 6 Hz), 3.37—3.65 (1 H, m), 3.93 (6 H, s), 6.89 (1 H, d, *J* 9 Hz), and 7.55 (1 H, broad s), 7.60 (1 H, d, *J* 9 Hz; further small splitting seen on one arm of signal).

An *N*-toluene-*p*-sulphonamide derivative was prepared: to a solution of compound (16) (50 mg) in pyridine (2 ml) was added toluene-*p*-sulphonyl chloride (100 mg) in pyridine (2 ml); the mixture was heated on a steam-bath for 30 min. After cooling, the reaction mixture was poured into dilute hydrochloric acid (30 ml). The product was extracted into ether. Evaporation of the dried ether solution gave an oil which crystallized from ethanol to give the *N*-toluenesulphonamide derivative, m.p. 108—110 °C (Found: C, 62.7; H, 6.35; N, 3.25; S, 7.95. $C_{21}H_{25}NO_5S$ requires C, 62.51; H, 6.24; N, 3.47; S, 7.95%).

2-(3,4-*Dimethoxyphenacyl*)-1-(3,4-*dimethoxystyryl*)*pyrrolidine* [*as* (12)].—3,′4′-Dimethoxy-2-pyrrolidin-2-ylacetophenone (210 mg, 0.84 mmol) and 3,4-dimethoxyphenylacetaldehyde [24] (250 mg, 1.39 mmol) were stirred in sodium-dried benzene (10 ml) for 1 h in the dark. The solvent was removed under reduced pressure to give 2-(3,4-*dimethoxyphenacyl*)-1-(3,4-*dimethoxystyryl*)*pyrrolidine* [as (12)] as a red oil; $\nu_{max.}$ (film) 1 678, 1 637, 1 598, 1 590, and 1 517 cm^{-1}; $\lambda_{max.}$ (MeOH) 279 and 303 nm; *m/z* 411.205 98 (M^+) ($C_{24}H_{29}NO_5$ requires *M*, 411.204 56), 395 [corresponds to structure (19)], 326 (reverse Diels-Alder reaction on *m/z* 395), 295, 258, 256, 246, 231, 230, 195, 180, 165, and 151; δ($CDCl_3$) 1.1—4.2 (9 H, m), 3.76 (12 H, s), 5.10 (1 H, d, J 14 Hz), and 6.6—7.6 (7 H, m).

(±)-*Septicine* (19).—3′,4′-Dimethoxy-2-pyrrolidin-2-ylacetophenone (210 mg, 0.84 mmol) and 3,4-dimethoxyphenylacetaldehyde (250 mg, 1.39 mmol) were stirred in sodium-dried benzene (10 ml) for 30 min in the dark. The solvent was removed under reduced pressure and the residual red oil was dissolved in dry methanol (10 ml). The solution was stirred in the dark for 2 h. (The same yield to septicine was obtained if the reactants were dissolved in dry methanol and stirred for 2 h, *i.e.* omission of the step involving benzene.) Sodium borohydride (60 mg) was added to the methanol solution and the mixture was stirred for 1 h. The reaction mixture was partitioned between chloroform and water and the aqueous layer was extracted several times with chloroform. The chloroform extracts were combined, dried, and evaporated to leave a brown oil (230 mg) which was purified by column chromatography using chloroform through to 20% methanol in chloroform as eluants. Further purification on preparative t.l.c. gave a colourless oil (66 mg, 20%) which was crystallized from acetonitrile–methanol, to give septicine, m.p. 132—134 °C (lit.,[10] 135—136 °C) $\lambda_{max.}$ (EtOH) (log ε), 235 (4.17) and 283 nm (4.02); *m/z* 395.209 38 (M^+) ($C_{24}H_{29}NO_4$ requires *M*, 395.209 65) and 326 (reverse Diels-Alder); δ($CDCl_3$) 1.2—4.1 (10 H, unresolved), 3.09 (1 H, d, *J* 16 Hz), 3.57 (3 H, s), 3.60 (3 H, s), 3.80 (6 H, s), 6.55 (2 H, s), and 6.67 (4 H, s); (Found: C, 73.1; H, 7.3; N, 3.45. Calc. for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54%). The synthetic septicine was identical by u.v., i.r., and mass spectrometry and by t.l.c. (Me_2CO, tetrahydrofuran, 2% MeOH in $CHCl_3$) with the natural material.

In a later experiment the procedure used for the synthesis of julandine [29] was followed using 1 equiv. of titanium(IV) chloride; sodium borohydride reduction was in propan-2-ol. A 29% yield of crystalline matrial (m.p. 135—137 °C) was obtained compared with a parallel experiment under the conditions described above which gave 17% (m.p. 134—137 °C).

(±)*Tylophorine* (1) [*from Septicine* (19)].—To a stirred solution of thallium(III) trifluoroacetate (60 mg, 0.12 mmol) in trifluoroacetic acid (5 ml) was added septicine (44 mg, 0.11 mmol). Stirring was continued for 20 min when the colour of the solution changed from green to brown. The mixture was poured into water (50 ml) and the aqueous solution was extracted thrice with chloroform. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate and were then dried. Evaporation gave a solid (44 mg) which was essentially pure tylophorine by t.l.c. (10% MeOH in $CHCl_3$). Chromatography of the tylophorine (2% MeOH in $CHCl_3$) gave pure synthetic alkaloid (41 mg, 95%); $\lambda_{max.}$ (EtOH) (log ε) 258 (4.61), 289 (4.32), 304 (4.07), 341 (3.17), and 358 nm (2.95); $\nu_{max.}$ ($CHCl_3$) 1 622 and 1 513 cm^{-1}; *m/z* 393.193 15 (M^+) ($C_{24}H_{27}NO_4$ requires *M*, 393.194 00) and 324.137 11 (reverse Diels–Alder fragmentation; $C_{20}H_{20}O_4$ requires *m/z* 324.136 15); δ($CDCl_3$) 1.4—3.8 (10 H, unresolved), 4.02 (6 H, s), 4.07 (6 H, s), 4.60 (1 H, d, *J* 15 Hz), 7.14 (1 H, s), 7.29 (1 H, s), 7.79 (2 H, s). The synthetic material was identical by t.l.c. (5 and 10% MeOH in $CHCl_3$) and by n.m.r., i.r., and u.v. spectrometry with natural tylophorine.

Reaction of Septicine with Two Equivalents of Thallium(III) *Trifluoroacetate*.—To a well-stirred solution of thallium(III) trifluoroacetate (60 mg, 0.12 mmol) in trifluoroacetic acid (5 ml) was added septicine (25 mg, 0.06 mmol). The solution first turned green then dark brown. After 15 min the solvent was removed under reduced pressure and the residue was taken up in chloroform. The chloroform solution was washed with water, dried, and evaporated to leave an oil which was purified by preparative t.l.c. (10% MeOH in $CHCl_3$) to give an oil (10 mg, 40%) which could be crystallized from ethanol–chloroform; $\lambda_{max.}$ (EtOH), 261, 270, 286, 303, 316, 347, and 366 nm; *m/z* 409.187 78 (M^+) ($C_{24}H_{27}NO_5$ requires *M*, 409.188 91), 394, 366, 340.131 78 ($C_{22}H_{20}O_5$ requires *m/z* 340.131 06), 325, 310, and 297;

δ($CDCl_3$) 1.0—4.0 (11 H, unresolved), 4.02 (3 H, s), 4.07 (3 H, s), 4.10 (6 H, s), 7.15 (1 H, s), 7.45 (1 H, s), and 7.80 (1 H, s). The same product was obtained on treating tylophorine with 1 equiv. of thallium(III) trifluoroacetate.

(*4-Methoxybenzoyl*)*acetic Acid*.—4-Methoxybenzoyl chloride [8.9 g, 88%; b.p. 135—137 °C/1 mmHg; $\nu_{max.}$ 1 770 cm^{-1} (C=O)] was prepared from 4-methoxybenzoic acid (9.0 g) and oxalyl chloride (7 ml) in dry benzene (100 ml) containing one drop of dimethylformamide at room temperature. Ethyl (4-methoxybenzoyl)acetate [34] was prepared in 90% yield exactly as described for ethyl (3,4 dimethoxybenzoyl)-acetate from 4-methoxybenzoyl chloride and ethyl acetoacetate. Alternatively it was prepared from monoethyl malonate (4.5 g) and 4-methoxybenzoyl chloride.[35] Aqueous alkaline hydrolysis gave 4-methoxybenzoylacetic acid (99%) under the same conditions as those described for (3,4-dimethoxybenzoyl)acetic acid above.

4′-Methoxy-2-pyrrolidin-2-ylacetophenone (17).—Reaction of 4-methoxybenzoylacetic acid with putrescine in the presence of diamine oxidase and catalase gave 4′-methoxy-2-pyrrolidin-2-ylacetophenone (88%); $\lambda_{max.}$ (EtOH) (log ε) 220 (3.91) and 276 nm (4.10); $\nu_{max.}$ (film) 1 675, 1 605, 1 589, and 1 513 cm^{-1}; *m/z* 219.125 99 (M^+) ($C_{13}H_{17}NO_2$ requires *M*, 219.125 92), 150, 135, 107, 84, 70, and 56; δ($CDCl_3$) 1.1—2.2 (4 H, unresolved), 2.54 (1 H, s, D_2O exchangeable), 2.7—3.2 (2 H, unresolved), 2.57 (2 H, d, *J* 6 Hz), 3.3—3.7 (1 H), 3.83 (3 H, s), 6.89 (2 H, d, *J* 9 Hz), and 7.92 (2 H, d, *J* 9 Hz). It could be converted into an *N*-toluene-*p*-sulphonamide, m.p. 102—104 °C (from EtOH) (Found: C, 64.35; H, 6.3; N, 3.9; S, 8.6. $C_{20}H_{23}NO_4S$ requires C, 64.32; H, 6.21; N, 3.75; S, 8.58%).

1-(*4-Methoxyphenyl*)-*2-pyrrolidin-2-ylethanol*.—4′-Methoxy-2-pyrrolidin-2-ylacetophenone was reduced with an excess of sodium borohydride in propan-2-ol at room temperature overnight to give 1-(4-methoxyphenyl)-2-pyrrolidin-2-ylethanol as a solid, m.p. 93—97 °C (from EtOH); $\nu_{max.}$ (Nujol) 3 500—3 000, 1 612, 1 587, and 1 510 cm^{-1}; $\lambda_{max.}$ (EtOH) (log ε) 229 (3.78), 277 (3.18), and 283 nm (3.10); *m/z* 221.145 00 (M^+) ($C_{13}H_{19}NO_2$ requires *M*, 221.141 57), 150, 135, 84, and 70; δ($CDCl_3$) 1.3—2.1 (6 H, unresolved), 2.94 (2 H, broad t, *J* 6 Hz), 3.35 (1 H, t, *J* 6 Hz), 3.79 (3 H, s), 4.01 (2 H, broad s, D_2O exchangeable), 4.96 (1 H, t, *J* 6 Hz), 6.96 (2 H, d, *J* 9 Hz), and 7.30 (2 H, d, *J* 9 Hz).

6-(*3,4-Dimethoxyphenyl*)-*1,2,3,5,8,8a-hexahydro*-7-(*4-methoxyphenyl*)*indolizine* (20).—Reaction of 3,4-dimethoxyphenylacetaldehyde and 4′-methoxy-2-pyrrolidin-2-ylacetophenone either in benzene (enamine formation seen in the n.m.r. spectrum) followed by treatment with titanium(IV) chloride and then sodium borohydride in propan-2-ol as described for julandine,[29] or by condensation in methanol without catalyst and then reduction as described for septicine above gave the indolizine (20) (22% or 62%, respectively) as an oil; $\lambda_{max.}$ (EtOH) (log ε) 232 (4.08) and 281 nm (3.89); $\nu_{max.}$ ($CHCl_3$) 1 610 and 1 512 cm^{-1}; *m/z* 365.199 14 (M^+) ($C_{23}H_{27}NO_3$ requires *M*, 365.199 08), 296, 281, and 265; δ($CDCl_3$) 1.4—2.2 (11 H, unresolved), 3.56, 3.70, and 3.78 (3 × 3 H, s), 6.49 (1 H, broad s), 6.65 (2 H, d, *J* 9 Hz), 6.66 (2 H, s), and 6.95 (2 H, d, *J* 9 Hz).

(±)-*Deoxytylophorinine* (34).—The indolizine (20) (51.2 mg) was oxidized with thallium(III) trifluoroacetate (76.0 mg) in trifluoroacetic acid (10 ml) as described above for tylophorine. The product obtained was shown by t.l.c. (10% MeOH in $CHCl_3$) to contain several components. Purification by column chromatography ($CHCl_3$ to 3% MeOH in $CHCl_3$) gave deoxytylophorinine (34) (18.3 mg, 36%). It was recrystallized from acetone, m.p. 206—210 °C (lit.,[28] 208—209 °C); $\lambda_{max.}$ (EtOH) (log ε) 260 (4.73) and 287 nm (4.49); $\nu_{max.}$ (Nujol) 1 620 and 1 512 cm^{-1}; *m/z* 363.183 32 (M^+) ($C_{23}H_{25}NO_3$ requires *M*, 363.183 43), 294, and 279; δ($CDCl_3$) 1.7—3.9 (9 H, unresolved), 3.64 (1 H, d, *J* 16 Hz), 4.02, 4.06, and 4.10 (3 × 3 H each, s), 4.62 (1 H, d, *J* 16 Hz). 7.21 (1 H, d, *J* 9 Hz), 7.26 (1 H, s), 7.46 (1 H, d, *J* 9 Hz), 7 89 (1 H, s), and 7.92 (1 H, s).

We thank the S.E.R.C. for studentships (F. B. J. and J. E. C.) and the University of Leeds for demonstratorships (C. J. M. and I. T. N.); we gratefully acknowledge the interest and financial support of Glaxo Research Ltd., Greenford, in an S.E.R.C. CASE project covering part of this work. We thank Dr. T. R. Govindachari for a sample of tylophorine and Dr. J. H. Russel for a sample of septicine.

[2/287 *Received*, 16*th February*, 1982]

REFERENCES

[1] For reviews see: T. R. Govindachari, 'The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1967, vol. 9, p. 517; T. R. Govindachari, *J. Indian Chem. Soc.*, 1973, **50**, 1; T. R. Govindachari and N. Viswanathan, *Heterocycles*, 1978, **11**, 587.

[2] R. A. Khatri, H. F. Schmitthenner, J. Shringarpure, and S. M. Weinreb, *J. Am. Chem. Soc.*, 1981, **103**, 6387; V. K. Mangla and D. S. Bhakuni, *Tetrahedron*, 1980, **36**, 2489.

[3] R. B. Herbert, F. B. Jackson, and I. T. Nicolson, *J. Chem. Soc., Chem. Commun.*, 1976, 865; R. B. Herbert and F. B. Jackson, *ibid.*, 1977, 955.

[4] J. H. Russel and H. Hunziker, *Tetrahedron Lett.*, 1969, 4035.

[5] T. R. Govindachari, M. V. Lakshmikantham, K. Nagarajan, and B. R. Pai, *Tetrahedron*, 1958, **4**, 311.

[6] T. R. Govindachari, B. R. Pai, S. Prabhakar, and T. S. Savitri, *Tetrahedron*, 1965, **21**, 2573.

[7] R. F. Borch, *Tetrahedron Lett.*, 1968, 61.

[8] H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Liebigs Ann. Chem.*, 1960, **632**, 38.

[9] B. Chauncey and E. Gellert, *Aust. J. Chem.*, 1970, **23**, 2503.

[10] J. H. Russel, *Naturwissenschaften*, 1963. **50**, 443; K. V. Rao, *J. Pharm. Sci.*, 1970, **59**, 1608.

[11] T. R. Govindachari, N. Viswanathan, J. Radhakrishnan, B. R. Pai, S. Natarajan, and P. S. Subramaniam, *Tetrahedron*, 1973, **29**, 891.

[12] T. Tanaka and I. Iijima, *Tetrahedron*, 1973, **29**, 1285; N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.*, 1972, **25**, 817.

[13] W. Bradley and R. Robinson, *J. Chem. Soc.*, 1928, 1310.

[14] W. B. Jakoby and J. Fredericks, *J. Biol. Chem.*, 1959, **234**, 2145.

[15] *cf.* C. Schöpf, *Angew. Chem.*, 1937, **50**, 797; C. Schöpf, F. Braun, K. Burkhardt, G. Dummer, and H. Müller, *Liebigs Ann. Chem.*, 1959, **626**, 123.

[16] F. Galinovsky, A. Wagner, and R. Weiser, *Monatsh. Chem.*, 1951, **82**, 551; E. F. L. J. Anet, G. K. Hughes, and E. Ritchie, *Aust. J. Sci. Res., Ser. A*, 1949, **2**, 616.

[17] A. J. Clarke and P. J. G. Mann, *Biochem. J.*, 1959, **71**, 596.

[18] J. M. Hill, 'Methods in Enzymology,' ed. H. and C. W. Tabor, 1971, vol. 17B, p. 730.

[19] F. B. Jackson, Ph.D. Thesis, University of Leeds, 1980.

[20] For examples see: P. Houdewind, J. C. L. Armande, and U. K. Pandit, *Tetrahedron Lett.*, 1974, 591; T. A. Spencer and K. K. Schmegel, *Chem. Ind. (London)*, 1963, 1765; W. D. Burrows and E. P. Burrows, *J. Org. Chem.*, 1963, **28**, 1180; L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, 1962, **95**, 1495.

[21] H. Böhme and G. Berg, *Chem. Ber.*, 1966, **99**, 2127; Y. Omote, T. Nakamura, K.-T. Kuo, and N. Sugiyama, *Nippon Kagaku Kaishi*, 1966, **87**, 888 (*Chem. Abstr.*, 1966, **65**, 16928).

[22] T. R. Govindachari and N. Viswanathan, *Tetrahedron*, 1970, **26**, 715.

[23] R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.

[24] Y. Ban and T. Oishi, *Chem. Pharm. Bull.*, 1958, **6**, 574; M. Barash and J. M. Osbond, *J. Chem. Soc.*, 1959, 2157.
[25] K. Kratzl and G. E. Miksche, *Monatsh. Chem.*, 1963, **94**, 434.
[26] A. McKillop, A. G. Turrell, and E. C. Taylor, *J. Org. Chem.*, 1977, **42**, 764; A. McKillop, A. G. Turrell, D. W. Young, and E. C. Taylor, *J. Am. Chem. Soc.*, 1980, **102**, 6504.
[27] E. C. Taylor, J. G. Andrade, and A. McKillop, *J. Chem. Soc., Chem. Commun.*, 1977, 538; E. C. Taylor, J. G. Andrade, G. J. H. Rall, and A. McKillop, *J. Am. Chem. Soc.*, 1980, **102**, 6513.
[28] N. B. Mulchandani and S. R. Venkatachalam, *Phytochemistry*, 1976, **15**, 1561.
[29] R. B. Herbert, *J. Chem. Soc., Chem. Commun.*, 1978, 794; J. E. Cragg and R. B. Herbert, following paper.
[30] S. H. Hedges and R. B. Herbert, *J. Chem. Res.*, 1979, (*S*) 1; (*M*) 410. J. E. Cragg, S. H. Hedges, and R. B. Herbert, *Tetrahedron Lett.*, 1981, **22**, 2127.
[31] B. J. Hunt and W. Rigby, *Chem. Ind.* (*London*), 1967, 1868.
[32] Z. J. Vejdělek and V. Trčka, *Chem. Listy*, 1955, **49**, 529 (*Chem. Abstr.*, 1956, **50**, 2621).
[33] H. Appel, W. Baker, H. Hagenbach, and R. Robinson, *J. Chem. Soc.*, 1937, 738.
[34] I. Shahak and Y. Sasson, *Tetrahedron Lett.*, 1973, 4207; H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, 1948, **70**, 2755.
[35] W. Wierenga and H. 1. Skulnick, *J. Org. Chem.*, 1979, **44**, 310.