SECTION C
Organic Chemistry

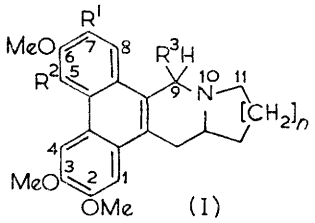
Cryptopleurine, a Synthesis based on Biogenetic Considerations

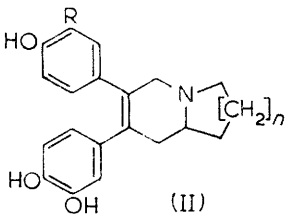
By **J. M. Paton, P. L. Pauson,* and T. S. Stevens,** Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow C.1

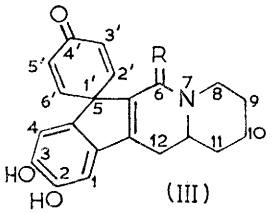
A ten-stage synthesis of (±)-cryptopleurine is described. In line with biogenetic postulates it involves oxidative coupling of 2-(3,4-dihydroxyphenyl)-*cis*-3-(4-hydroxyphenyl)quinolizidin-4-one (VII; $R^1 = H$, $R^2 = O$), itself obtained in six steps from 2-methylpyridine, methyl 3,4-dimethoxybenzoate, and 4-methoxyphenylacetyl chloride. The resulting dienone was found to have undergone dehydrogenation and, after rearrangement with acid, methylation, and reduction, afforded the alkaloid (I; $R^1 = R^2 = R^3 = H$; $n = 2$).

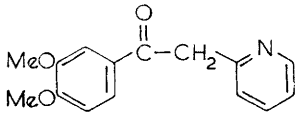
CRYPTOPLEURINE [1] (I; $R^1 = R^2 = R^3 = H$; $n = 2$) is the only known phenanthroquinolizidine alkaloid. Its nearest relatives are the four known phenanthroindolizidines,[2] tylophorine (I; $R^1 = OMe$, $R^2 = R^3 = H$; $n = 1$), tylocrebrine (I; $R^1 = R^3 = H$, $R^2 = OMe$; $n = 1$), tylophorinine (I; $R^1 = R^2 = H$, $R^3 = OH$; $n = 1$), and antofine [probably (I; $R^1 = R^2 = R^3 = H$; $n = 1$)]. Biogenetic schemes which involve intermediates of the type (II) have been discussed [2-4] for all these alkaloids. These suggestions are strengthened by the occurrence [5a] of the tetramethyl ether of the indolizidine (II; R = OH) in *Ficus septica* along with tylophorine and tylocrebrine, and the very recent finding [5b] † of the quinolizidine (VI; $R^1 = Me$, $R^2 = H_2$) along with cryptopleurine and (3,4-dimethoxyphenacyl)-piperidine. However, only Barton [4] has specifically considered the cyclisation of such intermediates. Unfortunately he inadvertently uses a formulation lacking the 6-methoxy-group of cryptopleurine and therefore considers dienol–benzene ‡ as well as dienone–phenol rearrangement of the phenolic coupling product, probably a dienone such as (III; $R = H_2$). Similar coupling to a dienone followed by rearrangement may be postulated in the formation of tylophorinine and antofine, whereas tylophorine and tylocrebrine, oxygenated in position 7 and 5, respectively, could arise directly from oxidative coupling of intermediates of the type (II) followed by methylation.

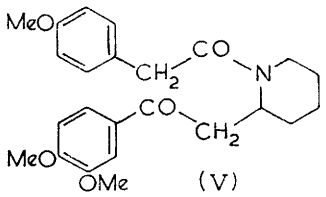
Although the structure of cryptopleurine was established by *X*-ray crystallographic methods [6] and confirmed [3b,7] by two syntheses *via* 9-bromo- or 9-chloromethyl-2,3,6-trimethoxyphenanthrene, a synthesis involving the oxidative coupling step of the biosynthetic scheme appeared worth undertaking. Development of additional synthetic methods is also necessary to make accessible a range of related compounds with a view to

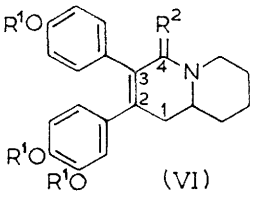

(I)


(II)


(III)


(IV)


(V)


(VI)

study of their biological activity. At least three of the alkaloids mentioned are known to be powerful vesicants, a property rare among other alkaloids, cryptopleurine [1] is a mitotic poison, possibly similar in action to colchicine, and tylocrebrine has been reported to have activity

† Dr. S. R. Johns has carried out a direct comparison of his naturally occurring with our synthetic sample and obtained indistinguishable i.r. and u.v. spectra. He also finds no depression in m.p., suggesting that the natural sample, though weakly optically active, is largely racemic.

‡ This would result in elimination of the oxygen atom at position 6 [in cryptopleurine (I)] and necessitate its re-introduction at a later stage.

[1] I. S. de la Lande, *Austral. J. Expt. Biol. Med. Sci.*, 1948, **26**, 181; E. Gellert and N. V. Riggs, *Austral. J. Chem.*, 1954, **7**, 113; E. Gellert, *ibid.*, 1956, **9**, 489; H. Hoffman, *Austral. J. Expt. Biol. Med. Sci.*, 1952, **30**, 541.

[2] For a recent review of this group and complete references see T. R. Govindachari in ' The Alkaloids,' ed. R. H. F. Manske, vol. 9, Academic Press, New York, 1967.

[3] (*a*) R. Robinson, ' The Structural Relations of Natural Products,' Clarendon Press, Oxford, 1955; (*b*) P. Marchini and B. Belleau, *Canad. J. Chem.*, 1958, **36**, 581; (*c*) E. Wenkert, *Experientia*, 1959, **15**, 165.

[4] D. H. R. Barton, *Proc. Chem. Soc.*, 1963, 293.

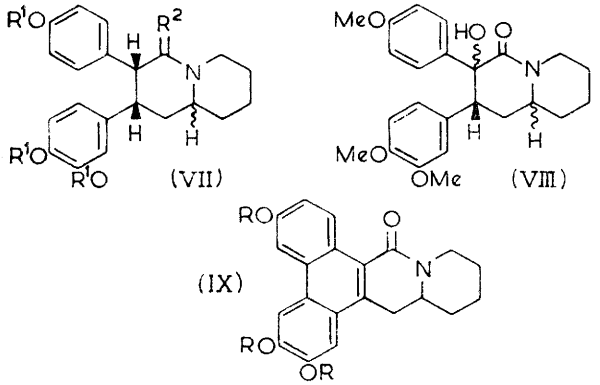
[5] (*a*) J. H. Russel, *Naturwiss.*, 1963, **50**, 443; (*b*) N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 2579; (*c*) J. W. Loder, *ibid.*, 1962, **15**, 296.

[6] L. Fridrichsons and A. McL. Mathieson, *Acta Cryst.*, 1955, **8**, 761.

[7] C. K. Bradsher and H. Berger, *J. Amer. Chem. Soc.*, 1957, **79**, 3287.

as an anti-leukemia agent.[8] A better understanding of the structure–activity relationships in this group is therefore desirable. With this object extensions of the following synthesis to yield analogues of cryptopleurine are in progress.

1-Methylpyridyl-lithium gave with methyl 3,4-dimethoxybenzoate 2-(3,4-dimethoxyphenacyl)pyridine (IV), and with 3,4-dimethoxybenzaldehyde the corresponding alcohol (IV; CHOH in place of CO). We did not obtain a quaternary ammonium salt on treatment of the ketone (IV) with *p*-methoxyphenacyl halides, while the alcohol appeared to suffer simultaneous dehydration. The ketone (IV) was readily hydrogenated over platinum. Preferential reduction of the pyridine ring occurred so that 2-(3,4-dimethoxyphenacyl)piperidine was isolated in good yield if the uptake of hydrogen was limited to 3 mol. The occurrence of this piperidine[9] and its desmethyl derivative, (4-hydroxy-3-methoxyphenacyl)piperidine, in natural alkaloids in two apparently unrelated plants which both produce cryptopleurine [*Cryptocarya pleurosperma*[5c] (family Lauraceae) and *Boehmeria platyphylla*[5b,9] (Urticaceae)] strongly suggests involvement of at least a closely related compound as an intermediate in the biogenesis of cryptopleurine. Further hydrogenation gave the corresponding alcohol which could be re-oxidised to the oxopiperidine with manganese dioxide. Attempts to form an *N*-(*p*-methoxyphenacyl) derivative were again unsuccessful, but *p*-methoxyphenylacetyl chloride readily yielded the expected amide (V). This was cyclised by potassium t-butoxide to the quinolizidinone derivative (VI; R^1 = Me, R^2 = O).



Reduction of the quinolizidinone (VI; R^1 = Me, R^2 = O) over palladium–charcoal afforded only one of the possible diastereoisomeric dihydro-derivatives (VII; R^1 = Me; R^2 = O). Hydrogenation may be assumed to cause *cis*-addition, but the relative configuration of the ring junction is not known. Epimerisation appeared to occur on heating with dry potassium t-butoxide in benzene, but only to the extent of 25—30%. Thus the two epimers appear to have comparable stability and no structural conclusions can be drawn. When air was not rigorously excluded, autoxidation rather than epimerisation was the main reaction and a tertiary alcohol, probably (VIII), was isolated.

Demethylation of the quinolizidinone (VII; R^1 = Me, R^2 = O) with aluminium bromide was incomplete, but with boron tribromide[10] the desired trihydric phenol (VII; R^1 = H, R^2 = O) was obtained in good yield. This product was best oxidised by manganese dioxide in the presence of silica gel,[11] and oxidation was accompanied by re-introduction of the 2,3-double bond, to give the dienone (III; R = O) (15—20%). This product should be available more directly *via* the unsaturated phenol (VI; R^1 = H, R^2 = O). However, demethylation of the corresponding ether (VI; R^1 = Me, R^2 = O) was less smooth than for the dihydro-derivative and the need to purify the phenol (VI; R^1 = H, R^2 = O) *via* its triacetate made this route no more attractive; it was therefore not investigated further.

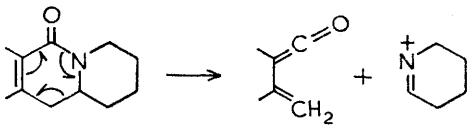
A mixture of acetic anhydride and sulphuric acid converted the dienone (III; R = O) into the triacetate of the desired trihydroxyphenanthroquinolizidinone (IX; R = Ac) which was treated with alkaline dimethyl sulphate to give the trimethyl ether (IX; R = Me). Finally lithium aluminium hydride reduction afforded (±)-cryptopleurine, indistinguishable by t.l.c. and u.v. and mass spectra from an authentic sample of the (−)-form provided by Dr. E. Gellert.

Most of the intermediates in this synthesis have been characterised by n.m.r. and mass spectra as well as u.v., i.r., and analytical data. Details are reported in the Experimental section, but a few features are worth mentioning here. The n.m.r. spectrum of the phenanthroquinolizidinone (IX; R = Ac) includes a very low-field doublet at τ 0·35 (J_{AB} 8 Hz) assigned to the 8-proton coupled to that at position 7 and strongly deshielded by the amide oxygen. This deshielding effect has been recorded for similarly situated protons, notably by Martin *et al.*[12] The appearance of sharp singlets (τ 1·7 and 2·2) corresponding to the 1- and 4-protons is evidence for the location of the acetoxy-groups at 2 and 3 [rather than 3 and 4] and hence confirms that the dienone (III; R = O) had been formed by *para–para* and not by *ortho–para* coupling. This dienone showed characteristic i.r. maxima at 166·0 and 161·5 mm.$^{-1}$ and u.v. absorption extending to 350 nm. The most characteristic fragmentation of the quinolizidinones, observed for the spirodienone (III; R = O) as well as the diaryl (VI; R^2 = O) and the phenanthro-derivatives (IX) is the expulsion of a C_5H_9N fragment from the parent ion (see Scheme).

Also described in the Experimental section are additional reduction products of the diarylquinolizidinone

[8] E. Gellert and R. Rudzats, *J. Medicin. Chem.*, 1964, **7**, 361.
[9] N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 1397.
[10] J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, 1968, **24**, 2289.
[11] B. Franck, H. J. Lubs, and G. Dunkelmann, *Angew. Chem. Internat. Edn.*, 1967, **6**, 969.
[12] R. H. Martin, N. Defay, F. Geerts-Evrard, P. H. Given, J. R. Jones, and R. W. Wedel, *Tetrahedron*, 1965, **21**, 1833.

(VI; R^1 = Me, R^2 = O). Lithium aluminium hydride reduced this amide to the corresponding amine (VI; R^1 = Me, R^2 = H_2), corresponding very closely in properties to the alkaloid to which this structure has



SCHEME

recently been assigned.[5b] This, on catalytic reduction, gave both epimeric dihydro-derivatives (VII; R^1 = Me, R^2 = H_2), in contrast to the reduction of the amide (VI; R^1 = Me; R^2 = O) to (VII; R^1 = Me, R^2 = O). The latter, as expected, gave only one of the dihydro-amines (VII; R^1 = Me, R^2 = H_2) on hydride reduction. In contrast to simpler *cis*-stilbene derivatives [13] neither the quinolizidine (VI; R^1 = Me; R^2 = H_2) nor the quinolizidinone (VI; R^1 = Me, R^2 = O) cyclised to the corresponding phenanthrene derivative on irradiation in cyclohexane solution.

In model experiments carried out before the synthesis described was undertaken, we were unable to effect intramolecular oxidative coupling of 3,4′-dihydroxybibenzyl. During the synthesis of the latter and attempts to synthesise other model compounds, the following new substances were obtained by routes described in the Experimental section: 3,4′-bisbenzyloxystilbene; 1-(4,5-dimethoxy-2-nitrophenyl)-2-(2-pyridyl)ethylene; 1-(3,4-dimethoxyphenyl)-6-(*p*-methoxyphenyl)hexanedione.

EXPERIMENTAL

Light petroleum refers to the fraction b.p. 60—80°. Molecular weights were obtained with an A.E.I. MS9 mass spectrometer. U.v. spectra were recorded for solutions in ethanol.

2-(3,4-*Dimethoxyphenacyl*)*pyridine* (IV).—To a well stirred ethereal solution of 2-methylpyridyl-lithium (0·1 mole) [prepared *via* phenyl-lithium from lithium ribbon (1·4 g.), bromobenzene (16 g.), and 2-methylpyridine (9·2 g.)] under nitrogen, at room temperature, was added methyl 3,4-dimethoxybenzoate (9·8 g., 0·05 mole) in ether (50 ml.). The mixture was heated under reflux for 1 hr., then treated with water (50 ml.) and 5N-hydrochloric acid (100 ml.) and separated. The red aqueous layer was poured into excess of sodium carbonate solution and the liberated base was extracted with chloroform. Evaporation of the solvent and rapid distillation of the residue *in vacuo* gave the *product*, b.p. 180—200°/0·5 mm., as a viscous oil (6·7 g., 54%) which solidified to a bright yellow solid, m.p. 58—60°, $\nu_{max.}$ (KCl) 167·5 mm.$^{-1}$ (CO) (Found: C, 70·2; H, 6·0; N, 5·4. $C_{15}H_{15}NO_3$ requires C, 70·1; H, 5·9; N, 5·4%). The compound gave a blue-green colour with alcoholic ferric chloride solution and formed a dark brown copper chelate, m.p. 161—163°. The *picrate* separated when ethanolic solutions of the components were mixed, and gave bright yellow needles, m.p. 180—182° (from aqueous ethanol) (Found: C, 51·7; H, 3·8; N, 11·4. $C_{21}H_{18}N_4O_{10}$ requires C, 51·8; H, 3·7; N, 11·5%). On dissolution in hot 25% hydrochloric acid, removal of picric acid by filtration and ether extraction, basification with sodium carbonate, and crystallisation from light petroleum, the picrate yielded a purified sample of the base, m.p. 60—62°.

Saturation of a solution of this base (IV) in ether–benzene with dry hydrogen chloride at 0° caused precipitation of the *hydrochloride*, as stout prismatic needles, m.p. 205—210° (decomp.) (from methanol–ether) (Found: C, 61·3; H, 5·6; N, 4·9. $C_{15}H_{16}ClNO_3$ requires C, 61·3; H, 5·5; N, 4·8%). Only the same hydrochloride was obtained from attempts to form a quaternary salt by heating the base in dimethylformamide–benzene with *p*-methoxyphenacyl chloride, bromide, or iodide.

1-(3,4-*Dimethoxyphenyl*)-2(2-*pyridyl*)*ethanol*.—The procedure of the preceding experiment was repeated with 3,4-dimethoxybenzaldehyde (16·6 g., 0·1 mole) in ether (80 ml.) in place of the benzoate. The dark gum obtained from the basic extract on evaporation was dissolved in hot ether. The crystalline *alcohol* slowly separated and gave white prisms (10·4 g., 42%), m.p. 86—87° (from ether–ethyl acetate), τ ($CDCl_3$) 6·9 (2H, d, *J* 7 Hz, $-CH_2-$), 6·15 (6H, s, OMe), 4·90 (1H, t, C*H*OH), 4·45br (1H, OH), 2·2—3·2 (6H, m, aromatic), and 1·55 (1H, m, pyridine 2-proton) (Found: C, 69·4; H, 6·7; N, 5·3. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%). Attempted quaternisation of this alcohol (2·59 g., 0·01 mole) by warming (40—50°) for 2 hr. with p-methoxyphenacyl chloride (1·84 g., 0·01 mole) in dry dimethylformamide (10 ml.), yielded (on cooling and dilution with ether) yellow prisms (700 mg.), m.p. 200° (decomp.), $\nu_{max.}$ (KCl) 1680 mm.$^{-1}$ (CO). Satisfactory analytical data were not obtained for this unstable salt, but its n.m.r. spectrum showed the absence of the CHOH·CH_2 group and was consistent with its formulation as 1-*p*-methoxyphenacyl-2-(3,4-dimethoxystyryl)pyridinium chloride.

2-(β-3,4-*Dimethoxyphenyl*-β-*hydroxyethyl*)*piperidine*.—The hydrochloride (1·8 g., 6·1 mmole) of the phenacylpyridine (IV) was dissolved in ethanol (50 ml.) and hydrogenated over platinum oxide (200 mg.) until hydrogen (4 mol.) had been absorbed (3 hr.). The filtered solution was evaporated and the residue was dissolved in water, made basic with sodium carbonate and extracted with chloroform. Evaporation of the chloroform layer gave the *imino-alcohol* (1·44 g., 95%) as white rosettes, m.p. 121—122° (from ethyl acetate–light petroleum) (Found: C, 67·9; H, 8·6; N, 5·3. $C_{15}H_{23}NO_3$ requires C, 67·9; H, 8·8; N, 5·3%).

2-(3,4-*Dimethoxyphenacyl*)*piperidine*.—(*a*) The preceding experiment was repeated, but interrupted after the uptake hydrogen (3 mol.). The ketone so obtained formed white prisms, m.p. 83—84° (from benzene–light petroleum), (lit.,[9] 81·5—82·5°), $\nu_{max.}$ (CCl_4) 332·0 (NH) and 167·0 (CO) mm.$^{-1}$ (Found: C, 68·1; H, 7·9; N, 5·3. Calc. for $C_{15}H_{21}NO_3$: C, 68·4; H, 8·0; N, 5·3%), τ (CCl_4) 8·52br (6H, CH_2 of piperidine, not adjacent to NH), 7·92 (1H, s, NH), 7·18br (5H, CH and CH_2 groups adjacent to NH and CO), 6·18 (6H, s, OMe), 3·35 (1H, s, *J* 8 Hz, 2-proton of aromatic ring), and 2·5 (2H, m, aromatic).

(*b*) 2-(β-3,4-Dimethoxyphenyl-β-hydroxyethyl)piperidine (2·65 g., 0·01 mole) in chloroform (80 ml.) was shaken with active manganese dioxide (10 g.) for 2 hr. at room temperature. The mixture was filtered, the residue was washed with chloroform, and the combined chloroform solutions were evaporated. Crystallisation of the residue yielded

[13] C. S. Wood and F. B. Mallony, *J. Org. Chem.*, 1964, **29**, 3373.

the ketone (2·1 g., 80%) identical with that described under (*a*).

2-(3,4-*Dimethoxyphenacyl*)-N-(4-*methoxyphenylacetyl*)-*piperidine* (V).—To the above ketone (2·63 g., 0·01 mole) and pyridine (0·8 g., 0·01 mole) in dry benzene (20 ml.), *p*-methoxyphenylacetyl chloride (1·84 g., 0·01 mole) was added. The mixture was set aside overnight at room temperature, pyridine hydrochloride was filtered off, and the filtrate was washed with dilute hydrochloric acid and water. Evaporation left the product as a pale brown gum (4·0 g., 95%), $\nu_{max.}$ (Nujol) 167·0 (ArCO) and 164·0 (>N·CO–) mm.$^{-1}$, which appeared homogeneous on t.l.c.

2-(3,4-*Dimethoxyphenyl*)-1,6,7,8,9,9a-*hexahydro*-3-(4-*methoxyphenyl*)*quinolizin*-4-*one* (VI; R^1 = Me, R^2 = O).—The keto-amide (V) (4·11 g., 0·01 mole) in dry benzene (40 ml.) was added to a stirred solution of potassium t-butoxide (1·12 g., 0·01 mole) in benzene (100 ml.) under nitrogen. The mixture was heated under reflux for 4 hr., poured into water (500 ml.), and separated, and the benzene layer was washed with 10% sodium hydroxide and water, then evaporated. The gummy residue was chromatographed on silica gel from which ether eluted the *quinolizinone* (VI; R^1 = Me, R^2 = O) (1·76 g., 45%), white needles (from chloroform–ether), m.p. 141—142°, $\nu_{max.}$ (KCl) 163·5 mm.$^{-1}$ (CO), $\lambda_{max.}$ 228 (log ε 4·35), 285 (3·98), and 320 (4·04) nm.; τ ($CDCl_3$) 6·52, 6·28, and 6·19 (each s, OMe) (Found: C, 73·3; H, 6·8; N, 3·5%; *M*, 393·1953. $C_{24}H_{27}NO_4$ requires C, 73·3; H, 6·9; N, 3·5%; *M*, 393·1940).

2-(3,4-*Dimethoxyphenyl*)-1,6,7,8,9,9a-*hexahydro*-3-(4-*methoxyphenyl*)*quinolizine* (VI; R^1 = Me, R^2 = H_2).—The lactam (VI; R^1 = Me, R^2 = O) (3·93 g., 0·01 mole), dissolved in ether–benzene (1 : 1; 80 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (2 g.) in ether (100 ml.). The mixture was heated under reflux for 4 hr., left overnight, then treated with crushed ice followed by saturated ammonium chloride solution (50 ml.). The ether layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue gave the *amine* (VI; R^1 = Me, R^2 = H_2) (2·8 g., 74%) as colourless needles, m.p. 136—137° (from benzene–ether), $\lambda_{max.}$ 235 (log ε 4·30) and 284 (3·97) nm. (Found: C, 75·9; H, 7·4; N, 3·7%; *M*, 379·2138. $C_{24}H_{29}NO_3$ requires C, 75·95; H, 7·7; N, 3·7%; *M*, 379·2147).

2-(3,4-*Dimethoxyphenyl*)-3-(4-*methoxyphenyl*)*quinolizidine* (VII; R^1 = Me, R^2 = H_2).—The amine (VI; R^1 = Me, R^2 = H_2) (3·79 g., 0·01 mole) in glacial acetic acid (40 ml.) and palladium–charcoal (200 mg., 10%) were stirred under hydrogen until uptake (1 mol.) was complete (4 hr.). The solution was then filtered, made basic with sodium carbonate, and extracted with chloroform. Evaporation of the extract left a gum, shown by t.l.c. to be a mixture of two components, (A) and (B) (R_F in 1 : 1 benzene–ether 0·57 and 0·10 respectively). Chromatography on silica gel afforded the two crystalline isomers of the *amine* (VII; R^1 = Me, R^2 = H_2). Isomer (A) (1·82 g.), eluted with and crystallised from ether–light petroleum (1 : 1) formed colourless needles, m.p. 117—118° (Found: C, 75·5; H, 8·2; N, 3·6%; *M*, 381·2309. $C_{24}H_{31}NO_3$ requires C, 75·5; H, 8·2; N, 3·7%; *M*, 381·2304). *Isomer* (B) (1·75 g.) was eluted with ether and crystallised from benzene–ether as colourless needles, m.p. 144—145° (Found: C, 75·5; H, 8·2; N, 3·7%; *M*, 381·2305).

2-(3,4-*Dimethoxyphenyl*)-cis-3-(4-*methoxyphenyl*)*quinolizidine*-4-*one* (VII; R^1 = Me, R^2 = O).—The unsaturated lactam (VI; R^1 = Me, R^2 = O) (3·95 g., 0·01 mole) and palladium–charcoal (200 mg.; 10%) in acetic acid (50 ml.) were stirred under hydrogen until 1 mol. had been absorbed (2 hr.). Isolation as in the preceding experiment yielded a single pure *dihydro-compound* (VII; R^1 = Me, R^2 = O) (3·75 g., 95%), white rosettes, m.p. 154—155° (from benzene–ether), $\nu_{max.}$ (KCl) 164·0 mm.$^{-1}$ (>N·CO–) (Found: C, 72·4; H, 7·4; N, 3·5%; *M*, 395·2095. $C_{24}H_{29}NO_4$ requires C, 72·8; H, 7·3; N, 3·5%; *M*, 395·2096). Lithium aluminium hydride reduction of this product afforded a base (65%) identical (m.p., mixed m.p., and i.r. spectrum) with isomer (A) of the preceding experiment.

2-(3,4-*Dimethoxyphenyl*)-trans-3-(4-*methoxyphenyl*)*quinolizidin*-4-*one*.—The *cis*-isomer (VII; R^1 = Me, R^2 = O) (0·98 g., 2·5 mmoles) was heated under reflux for 6 hr. with potassium t-butoxide (0·5 g.) in dry benzene under pure nitrogen. The mixture was poured into water and separated; the benzene layer was washed with dilute hydrochloric acid and water and then evaporated. The gummy residue was redissolved in ether. This solution deposited a white solid (0·32 g., 30%), m.p. 138—139° (from benzene–ether), shown by its mass spectrum to be isomeric with the starting material. Thin-layer chromatography showed that the mother liquors contained unchanged *cis*-isomer as well as two unidentified components.

2-(3,4-*Dimethoxyphenyl*)-3(?)-*hydroxy*-3-(4-*methoxyphenyl*)*quinolizidin*-4-*one* (VIII).—When the preceding experiment was carried out without careful exclusion of air, the *product* (0·54 g., 55%), isolated in the same manner, crystallised from ether as stout prisms, m.p. 145—146°, showing peaks attributable to a (tertiary) OH group in its i.r. [at 353·0, 139·0 and 110·0 mm.$^{-1}$ (KCl)] and n.m.r. spectra (τ 5·9, 1H, sharp s). The mass spectrum showed a molecular ion corresponding to $C_{24}H_{29}NO_5$ (Found: *M*, 411·2048. Required: *M*, 411·2046) and fragment ions including *M* – 18 ($C_{24}H_{27}NO_4$) and *M* – 135 (100%, 276·1598, $C_{16}H_{22}NO_3$ requires 276·1560), the latter arising by loss of $C_8H_7O_2$ (*M** 185·3) as a single unit, probably the *p*-MeO·C_6H_4·C·O group.

2-(3,4-*Diacetoxyphenyl*)-cis-3-(4-*methoxyphenyl*)*quinolizidin*-4-*one*.—To the lactam (VII; R^1 = Me, R^2 = O) (0·98 g., 2·5 mmoles) in benzene (10 ml.) was added a solution of freshly prepared aluminium bromide (2·7 g., 10 mmoles) in benzene (100 ml.) and the mixture was heated under reflux with stirring for 4 hr., then poured on ice. The precipitate was collected, washed with water, dried at 50° for 1 hr., and then acetylated by heating for 6 hr. in acetic anhydride (20 ml.) containing a few drops of pyridine. After decomposition of the excess of anhydride with water, extraction into chloroform, and evaporation, the *diacetate* (0·8 g., 72%) crystallised from benzene–ether as colourless needles, m.p. 189—190°, $\nu_{max.}$ (KCl), 1760 (Ac) and 1640 (>N·CO–) mm.$^{-1}$, τ ($CDCl_3$) 7·8 (6H, s, Ac) and 6·23 (3H, s, OMe) (Found: *M*, 451·1984. $C_{26}H_{29}NO_6$ requires *M*, 451·1995). The free phenol liberated from this diacetate gave a blue colour with Gibbs reagent (2,6-dichloroquinone chloroimide) and a greenish-blue colour with ferric chloride solution; the latter colour, which changed to deep blue on addition of sodium carbonate, is regarded as characteristic of a free catechol system.

2-(3,4-*Dihydroxyphenyl*)-cis-3-(4-*hydroxyphenyl*)*quinolizidin*-4-*one* (VII; R^1 = H, R^2 = O).—Boron tribromide [10] (2·5 g., 10 mmoles) was added dropwise at 0° to a stirred solution of the lactam (VII; R^1 = Me, R^2 = O) (0·98 g., 2·5 mmoles) in dry methylene chloride (50 ml.). The solution was then heated under reflux for 4 hr., cooled,

and poured on ice, and the precipitate was filtered off and washed with water. Crystallisation from methanol afforded the trihydric *phenol* (VII; R^1 = H, R^2 = O) (0·8 g., 90%) as colourless prisms, m.p. 290—294° (decomp.), $\nu_{max.}$ (KCl) 340·0 (OH) and 164·0 (>NCO–) mm.$^{-1}$, $\lambda_{max.}$ 214 (log ε 4·23), 225 (4·17), and 284 (3·67) nm. (Found: C, 71·2; H, 6·4; N, 3·9%. *M*, 353·1631. $C_{21}H_{23}NO_4$ requires C, 71·35; H, 6·6; N, 4·0%, *M*, 353·1627). Its *triacetate* formed colourless plates, m.p. 179—180° (from ether–light petroleum); the n.m.r. spectrum ($CDCl_3$) showed no peaks in the methoxy-group region (Found: C, 67·6; H, 6·0; N, 2·8. $C_{27}H_{29}NO_7$ requires C, 67·6; H, 6·1; N, 2·9%).

3-(4-*Acetoxyphenyl*)-2-(3,4-*diacetoxyphenyl*)-1,6,7,8,9,9a-*hexahydroquinolizin*-4-*one* (VI; R^1 = Ac, R^2 = O).—The lactam (VI; R^1 = Me, R^2 = O) was demethylated as described for its dihydro-derivative (VII; R^1 = Me, R^2 = O). The resulting phenol failed to crystallise and was therefore converted, with pyridine–acetic anhydride, into the *triacetate* (VI; R^1 = Ac, R^2 = O), m.p. 148—150°, the n.m.r. spectrum of which showed a 9H singlet for the acetoxy-protons (relative to 7 aromatic protons) and the absence of a methoxy-group (Found: *M*, 477·1813. $C_{27}H_{27}NO_7$ requires *M*, 477·1787). The mass spectrum showed progressive loss of 3 acetyl groups as C_2H_2O (42) the first such loss leading to $[C_{25}H_{25}NO_6]^+$ (Found: *M*, 435·1688; required 435·1682). Hydrolysis with methanolic potassium hydroxide again failed to yield crystalline phenol and although the crude product of its oxidation with manganese dioxide had a u.v. spectrum similar to that of the dienone described later, this route was not examined further.

2,3-*Dihydroxy*-6,7,8,9,10,11,11a,12-*octahydrospiro*{7-*azabenzo*[b]*fluorene*-5,1′-*cyclohexa*-2′,5′-*diene*}-4′,6-*dione* (III; R = O).—To the phenol (VII; R^1 = H, R^2 = O) (0·5 g.) in methanol (100 ml.) and chloroform (700 ml.) a mixture of silica gel (3 g.) and active manganese dioxide [14] (1 g.) was added with rapid stirring under nitrogen. After 1 hr., when a sample withdrawn from the mixture showed strong absorption at 250 nm., the mixture was filtered, the residue was washed with chloroform, and the combined solutions were evaporated *in vacuo*. The gummy residue was chromatographed on silica gel. Chloroform containing 2% ethanol eluted a fraction which crystallised when set aside in chloroform solution, yielding the *spirodienone* (III; R = O) (0·1 g. 20%) as fine colourless needles, m.p. 276—280° (decomp.) (from chloroform–ethanol), $\nu_{max.}$ (KCl) 166·0 (dienone), 163·5 (>N·CO–), and 161·5 (C=C) mm.$^{-1}$, $\lambda_{max.}$ 220 (log ε 4·33), 250 (4·37), 296 (3·63), and 350 (3·93) nm. (Found: *M*, 349·1306. $C_{21}H_{19}NO_4$ requires *M*, 349·1314). Attempts to effect this oxidation with ferricyanide, ferric chloride, or peroxidase were less successful.

2,3,6-*Triacetoxyphenanthro*[9,10-b]-11,12,13,14,14a,15-*hexahydroquinolizin*-9-*one* (IX; R = Ac).—Sulphuric acid (0·2 ml.) in acetic anhydride (1 ml.) was added to a suspension of the spirodienone (III; R = O) (100 mg.) in acetic anhydride (5 ml.) and the mixture was left for 24 hr. at room temperature, then poured on ice, neutralised with sodium carbonate, and extracted with chloroform. Evaporation of the extract *in vacuo* was followed by chromatography on silica gel. Elution with ether containing 1% ethanol yielded the *triacetate* (IX; R = Ac) (71 mg., 52%) as needles, m.p. 222—224° (from benzene–ether, then chloroform–ether), $\nu_{max.}$ (KCl) 176·0 (OAc) 163·5 (>N·CO–) mm.$^{-1}$, $\lambda_{max.}$ 243sh (log ε 4·67), 255 (4·68), 285sh (4·37), and 320 (4·07) nm. The aromatic protons gave rise to n.m.r. peaks ($CDCl_3$) at τ 2·61 [1H, dd, H-7 coupled (*J* 8 Hz) to H-8 and (*J* 2 Hz) to H-5], 2·2 [1H, s, H-1], 1·86 [1H, d, H-5], 1·7 [1H, s, H-4] and 0·35 [1H, d, H-8] (Found: *M*, 475·1633. $C_{27}H_{25}NO_7$ requires *M*, 475·1631).

2,3,6-*Trimethoxyphenanthro*[9,10-b]-11,12,13,14,14a,15-*hexahydroquinolizin*-9-*one* (IX; R = Me).—Dimethyl sulphate (5 ml.) was added dropwise, under nitrogen, to a stirred suspension of the triacetate (IX; R = Ac) (100 mg.) in 40% aqueous potassium hydroxide (10 ml.) and methanol (10 ml.). After the exothermic reaction had subsided, the mixture was heated under reflux for 2 hr., cooled, and poured into a large excess of water. The precipitate was collected, washed with water, and chromatographed on silica gel. Benzene–ether (1 : 1) eluted the *trimethyl ether* (IX; R = Me) (24 mg. 31%), straw-coloured needles, m.p. 194—195°, $\nu_{max.}$ (KCl) 1635 (NCO), $\lambda_{max.}$ 254 (log ε 4·57), 262 (4·56), 284 (4·35), and 338 (3·97) nm. (Found: *M*, 391·1778. $C_{24}H_{25}NO_4$ requires *M*, 391·1783). The mass spectrum included four metastable peaks corresponding to the successive loss from the parent ion (100%) at *m/e* 391 of C_5H_9N (*M** 242·6) ⟶ $C_{19}H_{16}O_4^+$ (Found: 308·1041; required 308·1049), CO(*M** 254·5) ⟶ $C_{18}H_{16}O_3^+$ (Found: 280·1099; required 280·1099) and CH_3 (*M** 250·8) ⟶ $C_{17}H_{13}O_3^+$ (Found: 265·0866; required 265·0865).

(±)-*Cryptopleurine* (I; R^1 = R^2 = R^3 = H; *n* = 2).—The compound (IX; R = Me) (40 mg.) in tetrahydrofuran (20 ml.) was added dropwise to lithium aluminium hydride (100 mg.) in the same solvent (50 ml.). The mixture was heated under reflux for 5 hr., hydrolysed with ammonium chloride solution, and extracted with ether. From the ether layer the basic material was extracted into 2N-hydrochloric acid, liberated by addition of sodium carbonate, and re-extracted into chloroform. Evaporation of the latter extract gave a gum (20 mg.) which was chromatographed on silica gel. Ether containing 1% methanol eluted a fraction which was further purified by preparative t.l.c. with benzene–methanol–ethyl acetate (8 : 1 : 1) in which the *product* (7 mg.) had the same R_F value (0·36) as an authentic sample of the (–)-form. The solid obtained from this purification also had u.v. spectrum identical with this sample [$\lambda_{max.}$ 258 (log ε 4·7), 287 (4·47), 345 (3·12), and 3·58 (2·97) nm.] and the same cracking pattern (high resolution mass spectrometry) (Found: *M*, 377·1986. $C_{24}H_{27}NO_3$ requires *M*, 377·1991). The most characteristic fragmentation is from the parent peak at 377 by loss of C_5H_9N (*M** 229·3) to $C_{19}H_{18}O_3^+$ (100%) (Found 294·1260; required 294·1256) and then CH_3 (*M** 264·8) to $C_{18}H_{15}O_3^+$ (Found 279·1014; required 279·1021).

3,4′-*Bisbenzyloxystilbene*.—As in the method [15] for the 2,4′-isomer, 4-benzyloxybenzyltriphenylphosphonium chloride [15] [prepared from 4-benzyloxybenzyl chloride] [16] (990 mg.) was added to a solution of sodium (46 mg.) in ethanol (50 ml.). 3-Benzyloxybenzaldehyde,[17] (424 mg.) in ethanol (25 ml.) was slowly added and the mixture was stirred for 24 hr. Filtration gave 3,4′-*bisbenzyloxystilbene*

[14] J. S. Belew and C. Tek-Ling, *Chem. and Ind.*, 1967, 1958.
[15] D. H. R. Barton, Y. L. Chow, A. Cox, and G. W. Kirby, *J. Chem. Soc.*, 1965, 3571.
[16] R. S. Shelton, M. G. Van Campen, D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen, and K. K. Wyckoff, *J. Amer. Chem. Soc.*, 1953, **75**, 5491.
[17] E. D. Bergmann and M. Sulzbacher, *J. Org. Chem.*, 1951, **16**, 84.

(310 mg., 40%) as colourless prisms, m.p. 148—149° (from benzene–light petroleum), $\lambda_{max.}$ 321 nm. (log ε 4·37) (Found: C, 85·6; H, 6·1. $C_{28}H_{24}O_2$ requires C, 85·7; H, 6·1%). Hydrogenation of this stilbene (1 g.) in ethanol (100 ml.) over 10% palladium–charcoal (200 mg.) for 5 hr. gave 3,4′-dihydroxybibenzyl (95%), m.p. 105—107° (lit.,[18] 106—108°).

1-(4,5-*Dimethoxy*-2-*nitrophenyl*)-2-(2-*pyridyl*)*ethylene*.—3,4-Dimethoxy-6-nitrobenzaldehyde (35 g., 0·174 mole) and 2-methylpyridine (25 ml., 0·2 mole) were heated under reflux in acetic anhydride (110 ml.) under nitrogen for 16 hr. The mixture was poured into warm water (1 l.) and after complete hydrolysis of the anhydride and cooling, the aqueous layer was decanted. Crystallisation of the tarry residue from ethanol (charcoal) afforded the *product* (19 g. crude; m.p. 159—165°; 7 g., 14%, pure) yellowish-brown prisms, m.p. 165—166°, $\lambda_{max.}$ (EtOH) 207, 272, 296, and 360 nm., $\nu_{max.}$ 158, 152, 127, 106, 79·5, 77, and 74 mm.$^{-1}$ (Found: C, 62·9; H, 4·9. $C_{15}H_{14}N_2O_4$ requires C, 62·8; H, 5·0%).

1-(3,4-*Dimethoxyphenyl*)-6-(4-*methoxyphenyl*)*hexanedione*.—δ-Anisoylvaleric acid [19] (23·6 g., 0·1 mole) was converted into the acid chloride (with excess of thionyl chloride in benzene) and the latter was added to veratrole (13·8 g., 0·1 mole) and dichloromethane (100 ml.). This mixture was cooled to −40° and stannic chloride (28·6 g., 0·11 mole) was added dropwise with stirring over 1 hr. The solution was then allowed to warm to room temperature during 2 hr. Addition to ice–hydrochloric acid was followed by separation, washing (Na_2CO_3 and H_2O) and drying of the organic layer which, on evaporation, left a gum which slowly crystallised. The *product* (5·3 g., 15%), white prismatic needles, m.p. 123—124° (from ethyl acetate) (Found: C, 70·55; H, 6·8; $C_{21}H_{24}O_5$ requires C, 70·7; H, 6·8%) was also obtained in similar yield by heating δ-anisoylvaleric acid (2·36 g., 10 mmole) and veratrole (1·52 g., 11 mmole) in polyphosphoric acid (30 g.) at 50° for 3 hr.

We thank Dr. E. Gellert for a sample of (−)-cryptopleurine. We also thank the S.R.C. for a research studentship (to J. M. P.), and Dr. P. Bladon and his staff for spectroscopic measurements.

[8/1919 *Received, December 30th,* 1968]

[18] A. Asahina and J. Asauo, *Ber.*, 1930, **63***B*, 429.
[19] D. Papa, E. Schwenk, and H. Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 308.