A BIOGENETICALLY PATTERNED SYNTHESIS OF DEOXYCRYPTOPLEURIDINE

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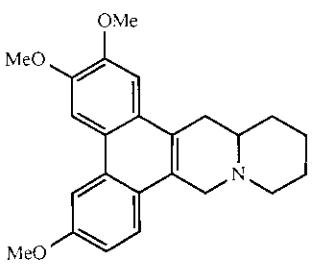
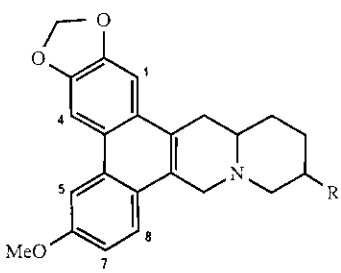
Abstract - The synthesis of two octahydroquinolizines (11) and (13) has been achieved following a biogenetically-patterned route. Oxidative cyclisation of (11) and (13) using thallium(III) trifluoroacetate gave the phenanthroquinolizidines (4) and (6), respectively, and also surprisingly (16) and (17), respectively. Careful comparison of the ^{1}H nmr spectra of (4) and (6) with those of the alkaloid cryptopleuridine and its acetate allowed confirmation that (2) is the correct structure for the alkaloid cryptopleuridine.

Cryptopleurine and cryptopleuridine are two alkaloids that have been isolated from the bark of Cryptocarya pleurosperma[1]. The structure of cryptopleurine (1) was established through X-ray analysis[2] and this has been confirmed in a number of syntheses[3,4]. The spectroscopic properties of cryptopleuridine suggested that it had a close structural relationship with cryptopleurine. Analysis of the ^{1}H nmr spectra of cryptopleuridine and its acetate (3) allowed the structure (2) to be assigned to the alkaloid[1]. An alternative structure (5) was not excluded by the spectral evidence but (2) was preferred on the biogenetic grounds that it



(1)



(2) R=OH
(3) R=OAc
(4) R=H

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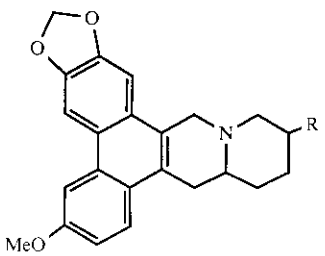
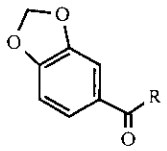
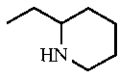
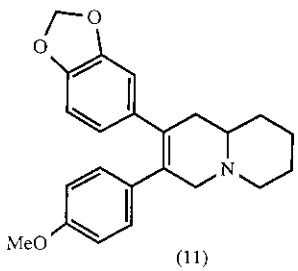


(5) R=OH
(6) R=H



(7) R=OH
(8) R=CH_2CO_2Et
(9) R=CH_2CO_2H

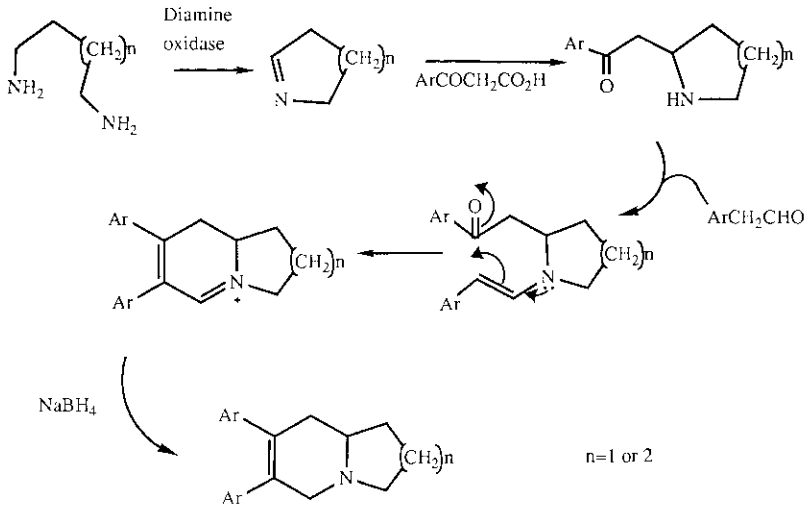
(10) R= 



(11)

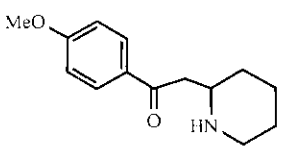
has the same aromatic substitution pattern as cryptopleurine (1). We report here a biogenetically patterned synthesis of the two alternatives, (4) and (6), for deoxycryptopleuridine and confirm that the structure (2) for cryptopleuridine is correct.

We have developed a simple, general synthetic route[3-5] (Scheme) to several phenanthroindolizidine alkaloids, e.g. tylophorine, and phenanthroquinolizidine alkaloids, e.g. cryptopleurine, which is based on their likely or established biosynthesis[3]. Application of this route to the elaboration of the quinolizidine (4) required the synthesis of 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone (10) as a key intermediate. This was achieved as follows. Reaction of 3,4-methylenedioxybenzoic acid (piperonylic acid) (7) with carbonyldiimidazole gave the corresponding imidazolide which on treatment with the magnesium salt of monoethyl malonate[6] afforded ethyl (3,4-methylenedioxybenzoyl)acetate (8). This ß-keto ester was also prepared by direct adaptation of a method described earlier[4,5]. Mild alkaline hydrolysis of the ß-keto ester (8) gave the corresponding acid (9). Incubation of this acid and 1,5-diaminopentane with pea-seedling diamine oxidase and catalase in phosphate buffer at pH 7 (cf. ref. 4) gave the desired 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone (10) in good preparative yield. Reaction of (10) with 4-methyoxyphenylacetaldehyde[4] followed by treatment of the intermediate enamine-ketone (Scheme) with silicon(IV) chloride (cf. ref. 4) and reduction with sodium borohydride gave the octahydroquinolizine (11); titanium(IV) chloride could be substituted for silicon(IV) chloride but it was experimentally a less convenient Lewis-acid catalyst. The overall reaction could also be achieved in dilute methanol solution without Lewis acid catalysis.



Scheme

The synthesis of (13) was achieved in an exactly similar way through the condensation of 4'-methoxy-2-(2-piperidyl)acetophenone (12) and 3,4-methylenedioxyphenylacetaldehyde.



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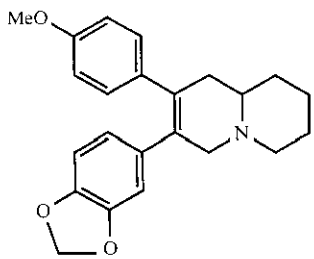
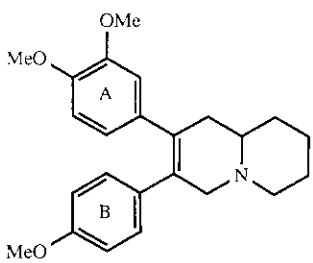


(13)



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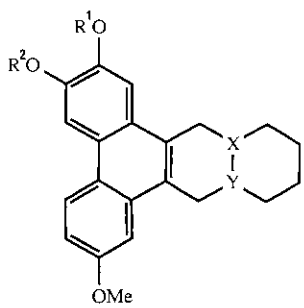


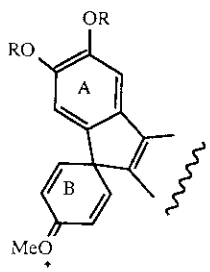
(15) R^1=R^2=Me, X=CH, Y=N

(16) R^1,R^2=CH_2, X=CH, Y=N

(17) R^1,R^2=CH_2, X=N, Y=CH

Thallium(III) trifluoroacetate has found useful application in effecting the linkage of two aromatic rings[7,8], and has been applied inter alia in the conversion of julandine (14) into cryptopleurine (1) in high yield[4]. Oxidation of (11) and (13) gave not just (4) and (6), respectively, as expected but to our surprise also (16) and (17), respectively, in an approximate ratio of 3:2. In the conversion of (14) into cryptopleurine (1) only a very small amount of the isomer (15) was obtained[4].

It is believed[7,8] that, in the coupling of two aromatic rings mediated by the thallium-(III) trifluoroacetate, oxidation occurs by transfer to thallium of a single electron from the ring with the lower oxidation potential [ring A in (14)], followed by electrophilic substitution of the radical-cation formed into the other aromatic ring, and further one-electron oxidation. The formation of (15) from julandine (14) was attributed[4] to the operation of a minor pathway for ring-closure which implicates (18). Rearrangement of (18) would afford (15) and also (1). But the major pathway here is the one which involves direct substitution of the radical-cation generated in ring A of (14) into ring B meta to the methoxy group, leading to the major product cryptopleurine (1). It would seem that, in the oxidative cyclisation of (11) and (13), the radical-cation derived from the ring with the methylenedioxy group is more stable[9] than the one derived from (14), which has two methoxy groups, and this radical-cation is more discriminating. The major pathway now involves the dienone (18), rearrangement of which affords the isomeric products observed.



(18)

The ^{1}H nmr spectra of the phenanthroquinolizidines (4) and (6) were closely similar but it is apparent (Table) that the chemical shift values for cryptopleuridine and its acetate (critically those for the protons on C-1 and C-8) most closely and clearly correspond to those of (4). This confirms that the structure of cryptopleuridine is indeed (2).

TABLE. Proton chemical shift values for cryptopleuridine acetate (3) and the phenanthroquinolizidines (4) and (6) in $CDCl_3$

Position:	1	4	5	7	8
(3)[a]	7.30	7.94	7.85	7.21	7.75
(4)[b]	7.32	7.93	7.82	7.17	7.75
(6)[b,c]	7.21	7.95	7.82	7.19	7.88

a: 100 MHz spectrum, methylenedioxy protons at 6.11 ppm; b: 400 MHz spectra; c: numbering according to that of (4).

The pattern of aromatic chemical shifts for (4) and (6) correlate with those published for phenanthroindolizidine and phenanthroquinolizidine alkaloids. All of these alkaloids bear aryl methoxy groups. Our data for a pair of compounds substituted by a methylenedioxy group will allow the secure assignment of structure to new alkaloids which are similarly substituted.

EXPERIMENTAL

All mp's were obtained on a hot-stage apparatus. Proton nmr spectra were obtained on a Perkin-Elmer R32 (90 MHz) or a Brüker AM400 (400 MHz), using $CDCl_3$ as solvent unless otherwise stated, with Me_4Si as internal standard. Mass spectra were recorded with Kratos MS25 or MS9/50 mass spectrometer. Ir spectra were recorded with a Perkin-Elmer 1420 spectrophotometer and UV-spectra were recorded with Pye Unicam PU 8800 spectrophotometer. Column chromatography was carried out using Kieselgel "G" - type 60 (Merck) and organic extracts were dried with magnesium sulphate.

Diamine Oxidase -- The enzyme was isolated from pea-seadlings following a published procedure[10]; it was purified to the stage prior to hydroxyapatite chromatography, resuspended in water, and kept frozen in 1-ml portions until required[4].

Ethyl (3,4-Methylenedioxybenzoyl)acetate (8) -- Magnesium ethoxide (4.90 g, 50 mmol) was added in one portion to a solution of monoethyl malonate[11] (13.2 g, 100 mmol) in anhydrous tetrahydrofuran (250 ml). The resulting mixture was stirred at room temperature for 1 h. The tetrahydrofuran was removed in vacuo and the gummy residue was triturated with ether to yield the magnesium salt of monoethyl malonate as a white solid (10.3 g).

Carbonyldiimidazole (1.80 g, 11 mmol) was added in one portion to a solution of 3,4-methylenedioxybenzoic acid (1.66 g, 10 mmol) in anhydrous tetrahydrofuran (50 ml) at room temperature. The resulting solution was stirred at 25°C for 6 h. The magnesium salt of monethyl malonate (3.15 g, 11 mmol) prepared above was added to this solution and the resulting mixture was stirred at 25°C for 18 h. The solvent was removed in vacuo. The residue was partitioned between ether (200 ml) and aqueous 0.5N HCl (200 ml) and the layers were separated. The aqueous phase was further extracted with ether (100 ml). The combined ether extracts were washed with aqueous saturated $NaHCO_3$ (200 ml), dried and filtered. The solvent was evaporated in vacuo to give ethyl (3,4-methylenedioxybenzoyl)acetate (1.77 g, 76%): δ ($CDCl_3$; 90 MHz) 1.25 (3H, t, J 8 Hz), 3.86 (2H, s), 4.17 (2H, q, J 8 Hz), 5.97 (2H, s), 6.88 (1H, d, J 9 Hz), 7.34 (1H, d, J 2 Hz), 7.45 (1H, dd, J 9 and 2 Hz); $\nu_{max.}$ (film) 1740 and 1680 cm^{-1}; $\lambda_{max.}$ (EtOH) 221, 272 and 307 nm; m/z 236.06843 (M^+, 18%) ($C_{12}H_{12}O_5$ requires M, 236.06847), 190 (6), 164 (6), 149 (100), 121 (13). (Found: C, 61.25; H, 5.1. Calc. for $C_{12}H_{12}O_5$: C, 61.02; H, 5.08%). This ester could also be prepared (in 50% yield) as described for ethyl (3,4-dimethoxybenzoyl)acetate[5].

(3,4-Methylenedioxybenzoyl)acetic Acid (9) -- A solution of ethyl (3,4-methylenedioxybenzoyl)acetate (1.675 g, 7.1 mmol) in aqueous potassium hydroxide (2.5%; 200 ml) was stirred for 48 h at room temperature. The solution was cooled in ice and then extracted with cold ether (3 x 75 ml). The aqueous solution was cooled to 5°C and acidified with ice-cold dilute sulphuric acid. Extraction with ether (5 x 75 ml), drying of the extracts and evaporation at room temperature gave (3,4-methylenedioxybenzoyl)acetic acid as a yellow solid (1.30 g, 86%) which was used without further purification in the next step.

3',4'-Methylenedioxy-2-(2-piperidyl)acetophenone (10) -- A solution of (3,4-methylenedioxybenzoyl)acetic acid (1.30 g, 6.25 mmol), cadaverine (1,5-diaminopentane) (0.1M aqueous solution, 63 ml) and potassium phosphate buffer (0.2M aqueous solution, pH 7, 20 ml) was prepared and the pH adjusted to 7. Catalase (0.5 mg) and pea-seedling diamine oxidase (2 ml; aqueous solution of activity 15 units ml^{-1}) were then added and the solution was incubated in 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 and washed with ether (3 x 100 ml). It was then basified with concentrated aqueous ammonia and extracted with chloroform (3 x 150 ml). Drying of the chloroform extract and evaporation of the solvent left an orange oily residue (0.785 g, 55%) of 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone which was essentially pure by tlc. This material was stored at -40°C and used for further reactions without purifiation. However, it could be recrystallized from acetone, mp 84-85°C. δ ($CDCl_3$; 90 MHz): 1.3-2.2

(6H, unresolved), 2.4 (1H, s, NH), 2.7-3.5 (5H, unresolved), 6.05 (2H, s), 6.80 (1H, d, J 9 Hz), 6.99 (1H, d, J 2.5 Hz), 7.55 (1H, dd, J 9 and 2.5 Hz); ν_{max} (Nujol) 3330, 1670 and 1605 cm^{-1}; λ_{max} (EtOH) 222, 271 and 304 nm; m/z 247.11998 (M^+, 22%), ($C_{14}H_{17}NO_3$ requires M, 247.12084), 164 (38), 149 (100), 121 (28), 84 (74); (Found: C, 67.85; H, 6.85; N, 5.45; Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.02; H, 6.88; N, 5.67%).

7-(4-Methoxyphenyl)-6-(3,4-methylenedioxyphenyl)-1,2,3,4,6,9,9a-octahydroquinolizine (11) -- A solution of 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone (10) (175 mg, 0.709 mmol) and 4-methoxyphenylacetaldehyde[4] (160 mg, 1.06 mmol) in dry benzene (4 ml) was stirred under nitrogen for 30 min. The solution was cooled in ice and silicon(IV) chloride (0.66 ml of a solution of 1.11 g, $SiCl_4$ in 5 ml of benzene) was added dropwise; a dark brown precipitate formed. The mixture was stirred at room temperature for 2 h and the benzene was then evaporated. Dry propan-2-ol (4.3 ml) was added to the residue, followed by sodium borohydride (46.8 mg) and the reaction mixture was stirred overnight. The solvent was evaporated and water followed by hydrochloric acid were added cautiously to the residue. The solution was extracted with ether and then basified with concentrated aqueous ammonia. Extraction with chloroform, followed by drying and evaporation of the solvent gave an oil (250 mg) which contained the required substance (11) as the major component by tlc. Chromatography with 10% MeOH in $CHCl_3$ gave a fraction, which on evaporation afforded a solid. Crystallization of this material from acetone gave pure (11) (103 mg, 40%), mp 156-157°C; δ ($CDCl_3$; 400 MHz) 1.35-2.5 (10H, partially resolved), 3.02 (1H, td, J 17 and 3 Hz), 3.08 (1H, broad d, J 11 Hz), 3.59 (1H, d, J 17 Hz), 3.78 (3H, s), 5.86 (2H, AB system, J 1.3 Hz), 6.48 (1H, dd, J 8 and 2 Hz), 6.51 (1H, d, J 2 Hz), 6.57 (1H, d, J 8 Hz), 6.68 (2H, d, J 9 Hz), and 6.96 (2H, d, J 9 Hz); λ_{max} (EtOH) 234 and 282 nm; m/z 363.18321 (M^+, 66%), ($C_{23}H_{25}NO_3$ requires M, 363.18343), 280 (100), 249 (28), 219 (13), 135 (22), 121 (19).

The octahydroquinolizine (11) was also prepared by the following method. A solution of 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone (10) (175 mg, 0.709 mmol) and 4-methoxyphenylacetaldehyde (100 mg, 1.06 mmol) in dry benzene (4 ml) was stirred under nitrogen for 30 min. The solvent was removed in vacuo and the residue was dissolved in dry methanol (1.2 l) to give a solution which was approximately 0.60 mM. The solution was stirred under nitrogen for 7 days. The solvent was then removed in vacuo. After reduction with sodium borohydride in propan-2-ol and the usual isolation procedure an oil was obtained (158 mg), which contained (11) as the major component.

6-Methoxy-2,3-methylenedioxyphenanthro[9,10-b]quinolizidine (4) and 7-Methoxy-2,3-methylenedioxyphenanthro[9,10-b]quinolizidine (16)-- To a stirred solution of the octahydroquinolizine

(11) (75 mg, 0.21 mmol) in trifluoroacetic acid (20 ml) was added thallium (III) trifluoroacetate (112.2 mg). After 30 min the mixture was added to water (20 ml). The mixture was basified with sodium carbonate and extracted with chloroform (3 x 20 ml). The chloroform extracts were dried and evaporated. Crystallization of the residue from acetone gave quinolizidine (4) together with the isomeric compound (16) (63 mg, 84%). These two compounds were separated by HPLC on a Spherisorb Si 5μ (10 mm i.d. x 25 cm) column; 95% (1:1 $CHCl_3$/hexane) and 5% ($CHCl_3$-0.25% N Et_3); 2 mm min^{-1}. The ratio of (4) to (16) in the crystalline mixture was found to be approx. 3:2. (4): δ ($CDCl_3$; 400 MHz) 1.35-3.8 (12H, partially resolved), 4.00 (3H, s), 4.45 (1H, d, J 15 Hz), 6.11 (2H, AB system, J 1.3 Hz), 7.17 (1H, dd, J 9 and 2.5 Hz), 7.32 (1H, s), 7.75 (1H, d, J 9 Hz), 7.82 (1H, d, J 2.5 Hz), and 7.93 (1H, s); $\lambda_{max.}$ (EtOH) 255 and 284 nm; m/z 361.16651 (M^+, 31%), ($C_{23}H_{23}NO_3$ requires M, 361.16778), 278 (100), 235 (4). (16): δ ($CDCl_3$; 400 MHz) 1.3-3.7 (13H, partially resolved), 3.97 (3H, s), 6.09 (2H, AB system, J 1.3 Hz), 7.14 (1H, d, J 2.5 Hz), 7.21 (1H, dd, J 9 and 2.5 Hz), 7.33 (1H, s), 7.93 (1H, s), and 8.39 (1H, d, J 9 Hz); $\lambda_{max.}$ (EtOH) 256 and 287 nm; m/z 361.16655 (M^+, 28%) ($C_{23}H_{23}NO_3$ requires M, 361.16778), 278 (100), 235 (5).

4'-Methoxy-2-(2-piperidyl)acetophenone (12) -- This compound was prepared from (4-methoxybenzoyl)acetic acid[5] and 1,5-diaminopentane in an exactly similar way to that described above for 3',4'-methylenedioxy-2-(2-piperidyl)acetophenone in approx. 60% yield, δ ($CDCl_3$; 90 MHz) 1.1-2.0 (6H, unresolved), 2.75 (1H, s, NH), 2.9-3.2 (5H, unresolved), 3.85 (3H, s), 6.85 (2H, d, J 8 Hz), 7.85 (2H, d, J 8 Hz); $\nu_{max.}$ (film) 3330, 1675, 1605, and 1580 cm^{-1}; $\lambda_{max.}$ (EtOH) 225 and 275 nm; m/z 233.14093 (M^+, 12%) ($C_{14}H_{19}NO_2$ requires M, 233.14157), 150 (10), 135 (52), 84 (100).

3,4-Methylenedioxyphenylacetaldehyde -- This compound was prepared from 3,4-methylenedioxybenzaldehyde via ethyl 2,3-epoxy-3-(3,4-methylenedioxyphenyl)propionate in an exactly similar way to that described for 4-methoxyphenylacetaldehyde[4]. Overall yield: 34%. Ethyl 2,3 epoxy-3-(3,4-methylenedioxyphenyl)propionate: δ ($CDCl_3$; 90 MHz) 1.35 (3H, t, J 7 Hz), 3.45 (1H, d, J 1.5 Hz), 4.05 (1H, d, J 1.5 Hz), 4.25 (2H, quartet, J 7 Hz), 6.05 (2H, s), and 6.80 (3H, m); $\nu_{max.}$ (film) 1740, 1600 and 1500 cm^{-1}. 3,4-Methylenedioxyphenylacetaldehyde: δ ($CDCl_3$; 90 MHz) 3.55 (2H, d, J 2 Hz), 5.90 (2H, s), 6.70 (3H, m), and 9.65 (1H, t, J 2 Hz); ν_{max} (film) 1720, 1600 cm^{-1}; m/z: 164.04661 (M^+, 39%) ($C_9H_8O_3$ requires M, 164.04734), 149 (13), 135 (100), 105 (8), 77 (17).

6-(4-Methoxyphenyl)-7-(3,4-methylenedioxyphenyl)-1,2,3,4,6,9,9a-octahydroquinolizine (13) -- Reaction of 4'-methoxy-2-(2-piperidyl)acetophenone with 3,4-methylenedioxyphenylacetaldehyde and treatment with silicon (IV) chloride followed by sodium borohydride as described above for

the octahydroquinolizine (11), gave (13) in good yield, mp 128-129°C (acetone). δ ($CDCl_3$; 400 MHz) 1.3-2.6 (10H, partially resolved), 3.02 (1H, td, J 17 and 3 Hz), 3.08 (1H, bd, J 11 Hz), 3.56 (1H, d, J 17 Hz), 3.73 (3H, s), 5.87 (2H, s), 6.51 (1H, dd, J 8 and 2 Hz), 6.53 (1H, d, J 2 Hz), 6.59 (1H, d, J 8 Hz), 6.67 (2H, d, J 9 Hz), 6.95 (2H, d, J 9 Hz); $\lambda_{max.}$ (EtOH) 235 and 282 nm; m/z 363.18358 (M^+, 61%) ($C_{23}H_{25}NO_3$ requires M, 363.18343), 280 (100), 249 (23), 219 (11), 135 (22), 121 (15).

3-Methoxy-6,7-methylenedioxyphenanthro[9,10-b]quinolizidine (6) and 2-Methoxy-6,7-methylenedioxyphenanthro[9,10-b]quinolizidine (17) -- Reaction of (13) in trifluoroacetic acid with thallium (III) trifluoroacetate as described above for (11) gave (6) and (17) in approx. 75% yield. The isomers (6) and (17) were separated by HPLC using the same column and solvent system as described for (4) and (16). (6): δ ($CDCl_3$; 400 MHz): 1.3-3.65 (12H, partially resolved), 4.00 (3H, s), 4.34 (1H, d, J 15 Hz), 6.10 (2H, s), 7.19 (1H, dd, J 9 and 2.5 Hz), 7.21 (1H, s), 7.82 (1H, d, J 2.5 Hz), 7.88 (1H, d, J 9 Hz), and 7.95 (1H, s); $\lambda_{max.}$ (EtOH): 235 and 288 nm; m/z 361.16725 (M^+, 34%) ($C_{23}H_{23}NO_3$ requires M, 361.16778), 278 (100), 235 (6). (17): δ ($CDCl_3$; 400 MHz): 1.3-3.65 (12H, partially resolved), 3.97 (3H, s), 4.31 (1H, d, J 15 Hz), 6.08 (2H, s), 7.21 (1H, s), 7.21 (1H, dd, J 9 and 2.6 Hz), 7.27 (1H, d, J 2.6 Hz), 7.94 (1H, s), 8.37 (1H, d, J 9 Hz); $\lambda_{max.}$ 256 and 286 nm; m/z 361.16762 (M^+, 31%) ($C_{23}H_{23}NO_3$ requires M, 361.16778), 278 (100), 235 (4).

ACKNOWLEDGEMENTS

We are grateful to Dr. S.R. Johns for providing us with ^1H nmr spectra of crytopleuridine and cryptopleuridine acetate. We thank the Association of Commonwealth Universities for the award of a fellowship (to V.P.) and Mr. R.J.S. Tatarek-Gintowt for the preparation of intermediates. We thank Dr. R.J. Bushby for his help.

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Received, 21st May, 1986