Alkaloid Studies. Part LXVI.[1] Reactions of Some *Aspidosperma* Alkaloids with *m*-Chloroperbenzoic Acid. Removal of the Angular Ethyl Group of Aspidospermine

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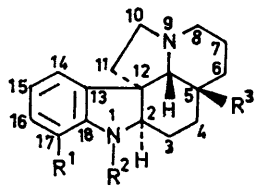
The oxidation of 20-oxoaspidospermine (6) and other *Aspidosperma* alkaloids (2c) and (13b) with *m*-chloroperbenzoic acid resulted in the formation of the 19-hydroxy-10-ketones (8a), (11a), and (14). Acetic anhydride–sulphuric acid treatment of (8a) afforded the 5(19)-en-10-one (9a), which with diborane gave *N*-deacetyl-5-deethylaspidospermine (10), an analogue of aspidospermine lacking the angular ethyl group. Alternative attempts to achieve this aim through degradation of the angular methoxycarbonyl group in cylindrocarine (2a) are also reported. The mass spectral fragmentation of several aspidospermine-type alkaloids has been studied with the aid of deuterium-labelled analogues.

In a continuing investigation of the alkaloids of the genus *Aspidosperma*, we reported recently the isolation, among others, of two novel alkaloids, deoxyaspidodispermine (1a) and aspidodispermine (1b) from *Aspidosperma dispermum*.[2] The two alkaloids are novel in that while they possess the skeleton of aspidospermine, they lack the angular ethyl group, which is replaced

[1] Part LXV, J. Kahrl, T. Gebreyesus, and C. Djerassi, *Tetrahedron Letters*, 1971, 2527.
[2] M. Ikeda and C. Djerassi, *Tetrahedron Letters*, 1968, 5837.

by a hydroxy-group. This is of considerable biogenetic interest in view of the estalished bio-origin of the 'C_9–C_{10}' unit in *Aspidosperma* alkaloids.[3]

We have also reported the isolation and characterization of twelve alkaloids from *Aspidosperma cylindrocarpon*.[4] These were mostly modifications of cylindrocarpine and cylindrocarpidine (and their 20-hydroxy-analogues), which had been isolated earlier[5] from the same plant. These alkaloids are biogenetically interesting in themselves, for they bear a highly oxygenated angular ethyl side chain which had not been encountered before among *Aspidosperma* alkaloids.[6] These alkaloids appeared to be good substrates for 'biogenetic-type' chemical entry into the aspidodispermine (1b) series, whereby the structures of the latter, which had been tentatively assigned on the basis of their chemical and spectral properties, could be established.



		R^1	R^2	R^3
(1)	a;	H	Ac	OH
	b;	OH	Ac	OH
	c;	OMe	Ac	OAc
(2)	a;	OMe	H	$CH_2{\cdot}CO_2Me$
	b;	OMe	H	$CH(OH){\cdot}CO_2Me$
	c;	OMe	Ac	$CH_2{\cdot}CO_2Me$
	d;	OMe	Me	$CH_2{\cdot}CO_2Me$
(3)	a;	OMe	H	$CH(OH){\cdot}CH_2{\cdot}OH$
	b;	OMe	Ac	$CH(OH){\cdot}CH_2{\cdot}OH$
(4)		OMe	Ac	CHO
(5)		OMe	Ac	CH_2OH
(6)		OMe	Ac	Ac
(7)	a;	OMe	H	CH(OH)Me
	b;	OMe	Ac	CH(OH)Me
(13)	a;	OMe	H	$CH_2{\cdot}CH_2{\cdot}OH$
	b;	OMe	Ac	$CH_2{\cdot}CH_2{\cdot}OAc$
	c;	OMe	Ac	$CH_2{\cdot}CH_2{\cdot}OH$
(16)		OMe	Ac	$CH_2{\cdot}CHO$
(17)	a;	OMe	H	$CH_2{\cdot}CH(OH)Ph$
	b;	OMe	Ac	$CH_2{\cdot}CH(OAc)Ph$
	c;	OMe	Ac	$CH_2{\cdot}CH(OH)Ph$
	d;	OMe	H	$CH_2{\cdot}CD(OH)Ph$
	e;	OMe	H	$CD_2{\cdot}CH(OH)Ph$
(18)	a;	OMe	H	CH=CHPh
	b;	OMe	Ac	CH=CHPh
(20)	a;	OMe	Ac	$CH_2{\cdot}COPh$
	b;	OMe	H	$CH_2{\cdot}COPh$

20-Hydroxycylindrocarine (2b) was reduced with lithium aluminium hydride; the resulting compound showed physical and spectral properties consistent with the diol structure (3a). The crude diol (3a) was acetylated with pyridine–acetic anhydride and partially hydrolysed with alkali to give the *N*-acetyl diol (3b). Cleavage with periodic acid in aqueous tetrahydrofuranol gave the crystalline aldehyde (4), whose i.r., u.v., n.m.r., and mass spectra were consistent with its assigned structure.

Oxidation of aldehyde (4) with *m*-chloroperbenzoic acid did not lead (by Baeyer–Villiger oxidation) to a formate but rather to a highly polar compound whose mass spectrum showed an increase of 16 mass units and a fragmentation pattern which suggested the genesis of an N_b-oxide. On reduction with Raney nickel[7] the compound afforded two products. The major one was the starting aldehyde (4); spectra of the minor one showed the presence of a hydroxy-group [$\nu_{max.}$ ($CHCl_3$) 3610 and 3400 cm^{-1}] and an increase of two mass units. Its structure (5) was confirmed when the alcohol obtained by sodium borohydride reduction of aldehyde (4) showed identical physical and spectral properties.

Since the Baeyer–Villiger reaction with methyl ketones occurs with relative ease,[8] it was felt desirable to prepare ketone (6). Addition of methylmagnesium iodide to the aldehyde (4) gave a mixture of the alcohols (7a and b), with (7b) as the major product; (7a) was converted into (7b) by acetylation and partial hydrolysis. Moffat oxidation[9] of the alcohol (7b) gave a compound whose i.r., u.v., n.m.r., and mass spectra were consistent with structure (6).

Oxidation of ketone (6) with *m*-chloroperbenzoic acid gave two isolable products. The major product was highly polar, and was the N_b-oxide, for it reverted to the ketone (6) on treatment with aqueous iron(II) sulphate.[10] T.l.c. comparison of the second product with authentic 17-*O*-methylaspidodispermine acetate (1c) (the expected Baeyer–Villiger oxidation product) and aspidodispermine (1b) showed it to be more polar than either. High resolution mass spectrometry established its molecular composition as $C_{22}H_{26}N_2O_5$ [*cf.* $C_{19}H_{24}N_2O_3$ for (1b)].

Its u.v. spectrum was similar to that of the ketone (6). The n.m.r. spectrum (Figure 1), however, showed a few changes: the methyl singlet at δ 1·96 for ketone (6) was shifted downfield to δ 2·10 p.p.m., an exchangeable one-proton singlet appeared at δ 6·28, the two-proton signal for ketone (6) at δ 3·0—3·32 had disappeared, and new two-proton AB doublets (*J* 16 Hz) had appeared at δ 2·42 and 2·64. The mass spectrum showed a gain of 30 mass units but the fragmentation pattern is markedly different from those of ketone (6)

[3] For recent reviews see (*a*) A. I. Scott, *Accounts Chem. Res.*, 1970, **3**, 151; (*b*) E. Leete, *ibid.*, 1969, **2**, 59; (*c*) A. R. Battersby, *Pure Appl. Chem.*, 1967, **14**, 117 and references in these papers.

[4] B. V. Milborrow and C. Djerassi, *J. Chem. Soc.* (*C*), 1969, 417.

[5] C. Djerassi, A. A. P. G. Archer, and T. George, *Tetrahedron*, 1961, **16**, 212.

[6] M. Hesse, 'Indolalkaloide in Tabellen,' Ergänzungwerk, Springer-Verlag, Berlin, 1968; B. Gilbert in 'The Alkaloids,' Academic Press, New York, 1968, vol. XI, ch. 9.

[7] E. Hayashi, H. Yamanaka, and K. Shimizu, *Chem. and Pharm. Bull.* (*Japan*), 1959, **7**, 141.

[8] C. H. Hassall, *Org. Reactions*, 1957, **9**, 73.

[9] K. E. Pfitzner and J. G. Moffat, *J. Amer. Chem. Soc.*, 1963, **85**, 3027; 1965, **87**, 5661, 5670; J. D. Albright and L. Goldman, *J. Org. Chem.*, 1965, **30**, 1107. The improved Moffat oxidation (J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, 1965, **87**, 4214) however, gave a large amount of the methyl thioether as a side product.

[10] D. W. Thomas, A. Achenbach, and K. Biemann, *J. Amer. Chem. Soc.*, 1966, **88**, 3423.

and other aspidospermine-type alkaloids.[11] The i.r. spectrum showed a new absorption at 1700 cm.$^{-1}$; this and the n.m.r. evidence suggested a five-membered lactam system.[12] This feature and the presence of a hydroxy-group (i.r. and n.m.r. spectra) accounts for the gain of 30 mass units. All these data are consistent with structure (8a), which also accounts for the unusual mass spectral fragmentation pattern; substitution at C-10 is known to have a marked effect on the mass spectra of many aspidospermine-type alkaloids.[11a]

At this juncture the structure of aspidodospermine (1b) was established in our laboratory[13] by *X*-ray

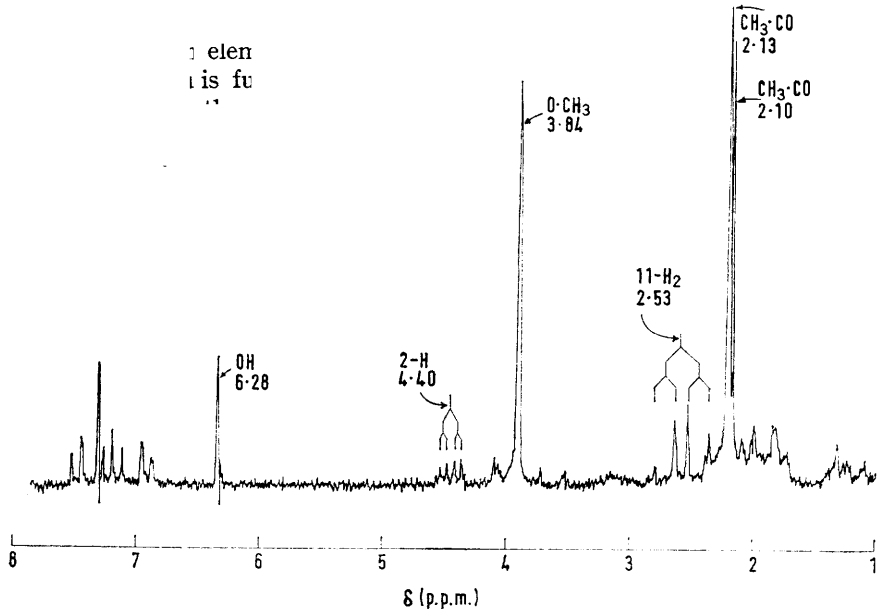


FIGURE 1 N.m.r. spectrum of the hydroxy-keto-lactam (8a)

crystallography. Thus synthetic verification of the structures (1a) and (1b) was no longer necessary, but the peroxy-acid oxidation studies were continued.

The ketone (6) was oxidised with chromium trioxide in pyridine;[12] the major product isolated (8b) had i.r., u.v., n.m.r., and mass spectra similar to those of the hydroxy-keto-lactam (8a) except for the lack of i.r. hydroxy-absorption at 3380 cm^{-1} and of a hydroxy-proton signal in the n.m.r. spectrum. Treatment of the keto-lactam (8b) with *m*-chloroperbenzoic acid failed to give (8a), thus showing that hydroxylation of ketone (6) occurs prior to oxidation to the lactam.*

To determine fully the structure of compound (8a), unambiguous location of the hydroxy-group was required. Attempts to acetylate the hydroxy-keto-lactam (8a), even at elevated temperatures, failed. However, treatment with acetic anhydride and catalytic amounts of sulphuric acid gave a product ($C_{20}H_{22}N_2O_3$) whose i.r. spectrum was similar to that of the hydroxy-keto-lactam (8a) except for the lack of hydroxy-absorption at 3380 cm^{-1}. The n.m.r. spectrum (Figure 2) also showed no hydroxy-proton signal and lacked the methyl singlet at δ 2·10 p.p.m. The mass spectrum showed a molecular ion at *m/e* 338, corresponding to a loss of 60 mass units ($C_2H_4O_2$) from (8a); otherwise the fragmentation pattern was similar. These data are consistent with structure (9a), which could arise from (8a) *via* a carbonium ion which is attacked by water and eliminates the elements of acetic acid (Scheme). The structure (9a) is further supported by the assignment of almost all the signals in the n.m.r. spectrum (Figure 2) taken with a europium shift reagent.[15] This places the hydroxy-group at C-19 in the hydroxy-keto-lactam (8a)—an assumption which was confirmed by further chemical studies.

All attempts at reducing either the carbonyl group or the double bond of the enamide (9a), by sodium borohydride and glacial acetic acid,[16a] by lithium

* Although amine oxides have been oxidised to lactams with aqueous potassium dichromate[14a] or rearranged to carbinolamines with acids,[14b] it is not obvious how the hydroxy-keto-lactam (8a) is formed under the conditions employed in this investigation.

[11] H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Structure Elucidation of Natural Products by Mass Spectrometry,' vol. 1, Holden-Day, San Francisco, 1964, (*a*) p. 124; (*b*) p. 102.

[12] (*a*) H. Conroy, P. R. Brook, and Y. Amiel, *Tetrahedron Letters*, 1959, 4; (*b*) M. F. Bartlett and W. I. Taylor, *J. Amer. Chem. Soc.*, 1960, **82**, 5941.

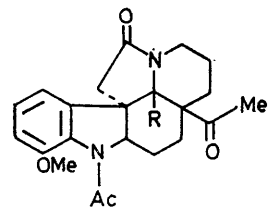
[13] N. C. Ling and C. Djerassi, *Tetrahedron Letters*, 1970, 3015.

[14] (*a*) P. J. Scheuer, W. I. Kimoto, and K. Ohinata, *J. Amer. Chem. Soc.*, 1953, **75**, 3029 and references therein; (*b*) R. H. F. Manske and H. L. Holmes, 'The Alkaloids,' vol. 1, Academic Press, New York, 1950, p. 413.

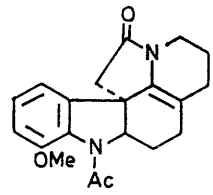
[15] J. K. M. Sanders and D. H. Williams, *Chem. Comm.*, 1970, 422.

[16] (*a*) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, 1963, **28**, 421; (*b*) W. G. Brown, *Org. Reactions*, 1951, **6**, 469; (*c*) N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, 1968, **79**, 6210.

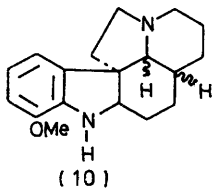
aluminium hydride,[16b] by formic acid,[16c] or by hydrogenation, were unsuccessful. Treatment with *m*-chloroperbenzoic acid failed to give the desired epoxide. Hydrolysis with acid gave an intractable mixture, but alkaline hydrolysis led to the *N*-deacetyl enamide (9b), which could be reduced with diborane[17] to a separable mixture



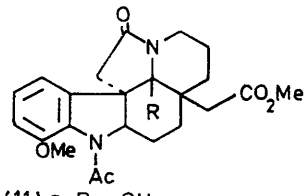
(8) a; R = OH
b; R = H



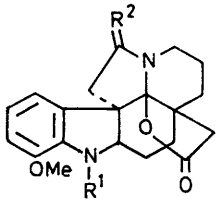
(9) a; R = Ac
b; R = H



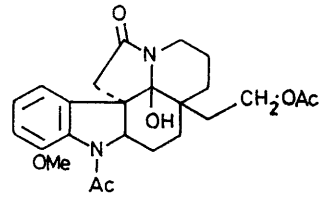
(10)



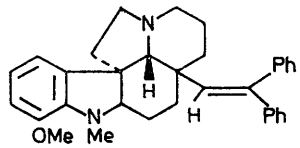
(11) a; R = OH
b; R = H



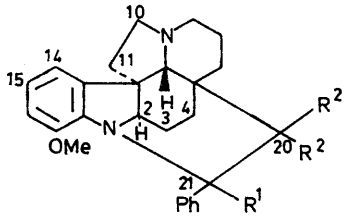
(12) a; R^1 = Ac, R^2 = O
b; R^1 = H, R^2 = H_2



(14)



(15)



(19) a; R^1 = H, R^2 = H
b; R^1 = D, R^2 = H
c; R^1 = H, R^2 = D

of four compounds. The major product (10) ($C_{18}H_{24}N_2O$) displayed a mass spectrum (Figure 3) with essentially the same fragmentation pattern as deacetylaspidospermine,[18] except for the mass changes associated with

[17] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.

[18] K. Biemann, 'Mass Spectrometry; Organic Chemical Applications,' McGraw-Hill, New York, 1962, p. 315.

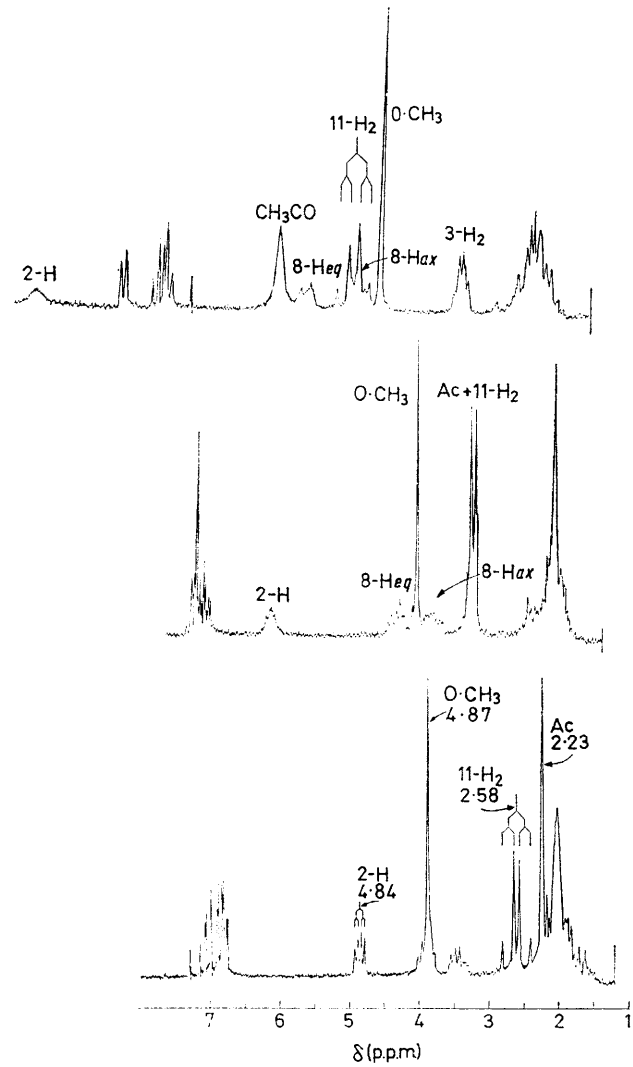
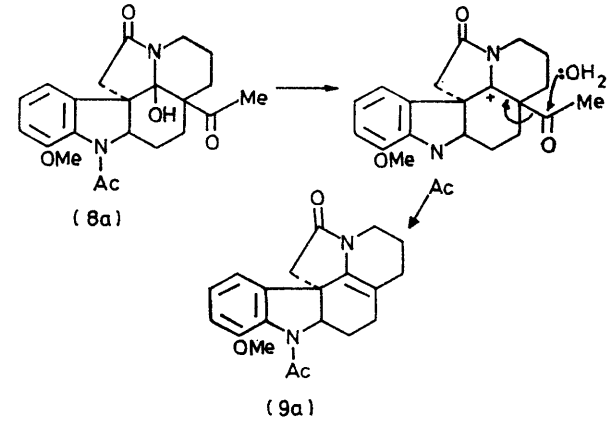


FIGURE 2 N.m.r. spectrum of the enamide (9a) (a) without the europium shift reagent; (b) and (c) with the shift reagent [(c) with more of the shift reagent than (b)]

the lack of the angular ethyl group. The peaks corresponding to *m/e* 284, 124, and 152 in deacetylaspidospermine appeared 28 mass units lower, and the ions



(8a)

(9a)

SCHEME Mechanism of the formation of enamide (9a)

at *m/e* 160 and 174 containing the indole system appeared at the same mass number. The three other products, which were obtained in minute quantities, exhibited almost identical spectra, indicating that they are isomers. Though all four isomers exhibited substantial $M - 1$ peaks, two showed a smaller peak than the other two [which included (10)]. This may indicate the stereochemistry of amine (10) at C-19 features which would especially facilitate oxidation at C-10 or C-19, the peroxyacid oxidation was carried out on the more abundant cylindrocarine (2a). For this purpose cylindrocarine (2a) was acetylated to give cylindrocarpidine (2c) and then oxidized with *m*-chloroperbenzoic acid to give two main products. One of them was the N_b-oxide; on treatment with aqueous iron(II) sulphate it was reduced back to cylindrocarpidine (2c).

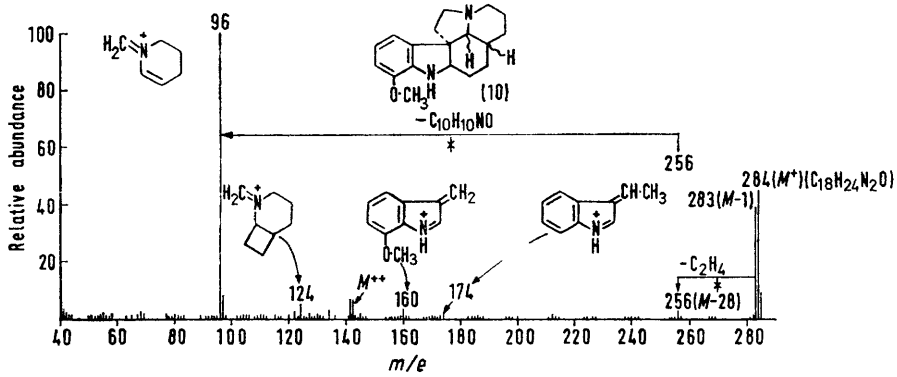


FIGURE 3 Mass spectrum of the amine (10)

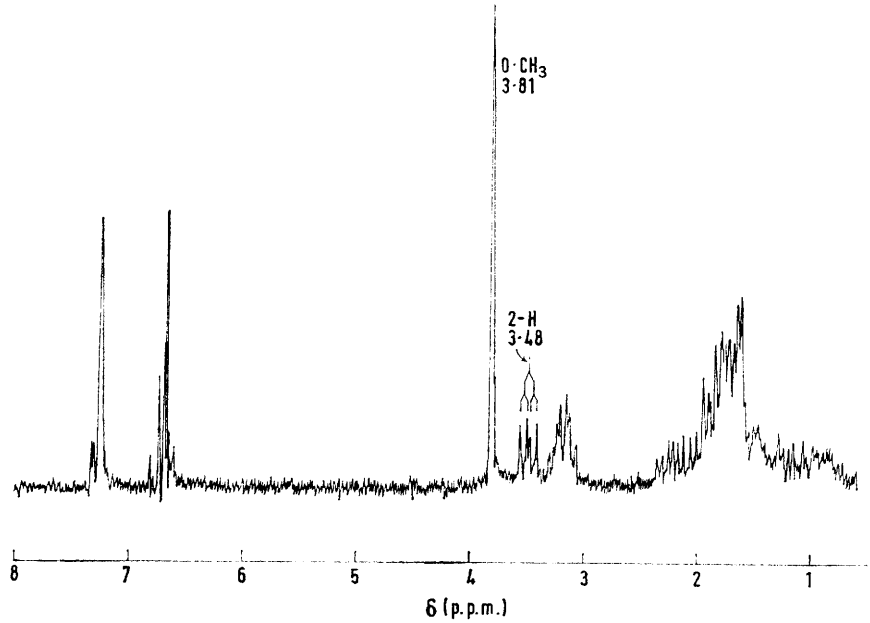


FIGURE 4 N.m.r. spectrum of the amine (10)

may be opposite to that of aspidospermine, since it is known that formation of the $M - 1$ peak is highly dependent on the stereochemistry at C-19.[11b]

The i.r. spectrum showed absorption at 3360 cm^{-1} (N–H) and no carbonyl absorption. The n.m.r. spectrum (Figure 4) was very similar to that of *N*-deacetylaspidospermine, with the marked absence of the ethyl side-chain signals at δ *ca.* 0·65 p.p.m.[19] These data are consistent with structure (10) for the diborane reduction product of the enamide (9b).

Since ketone (6) does not possess any structural The other was a crystalline solid whose i.r. spectrum showed new absorption bands at 3290 (OH) and 1700 cm^{-1} (five-membered lactam). The u.v. spectrum was essentially the same as that of cylindrocarpidine (2c). The n.m.r. spectrum showed an exchangeable hydroxy-proton at δ 5·64, two-proton AB doublets (J 16 Hz) at δ 2·38 and 2·60 (CH_2·CO), and another pair of AB doublets (2H, J 16 Hz) at δ 2·19 and 2·59 (CH_2·CO). The two C-10 protons shown at δ 3·11 in the n.m.r. spectrum of cylindrocarpidine had disappeared. The

[19] A. Walser and C. Djerassi, *Helv. Chim. Acta*, 1965, **48**, 391.

mass spectrum showed the molecular composition $C_{23}H_{28}N_2O_6$ and a fragmentation pattern different from that of cylindrocarpidine. All these data can be accommodated by structure (11a).

Reaction of the hydroxy-lactam (11a) with acetic anhydride–pyridine at room temperature failed to give the acetate, but on refluxing the mixture overnight a product was obtained whose i.r. absorption at 1770 cm^{-1} indicated a five-membered lactone. This feature was confirmed both by the mass spectrum, which showed the composition $C_{22}H_{24}N_2O_5$, and the n.m.r. spectrum, which lacked the hydroxy-proton signal at δ 5·64 and the singlet at δ 3·60 ($O{\cdot}CH_3$). The compound was formulated as (12a) and its structure was proven by partial synthesis (acetylation and chromium trioxide–pyridine oxidation) from *N*-deformyldichotamine (12b).[20] This also proves that the hydroxy-group in the hydroxy-lactams (8a) and (11a) must be attached to C-19.

Oxidation of cylindrocarpidine (2c) with chromium trioxide–pyridine gave the known 10-oxocylindrocarpidin (11b).[21] *m*-Chloroperbenzoic acid failed to oxidise the latter to the hydroxy-lactam (11a), consistent with the previous negative result on the keto-lactam (8b).

In order to avoid lactone formation, the peroxyacid oxidation was carried out on *N*-acetyl-21-*O*-acetylcylindrocarpinol (13b), which was prepared by lithium aluminium hydride reduction of cylindrocarine (2a) to cylindrocarpinol (13a) * and acetylation. The *m*-chloroperbenzoic acid oxidation of (13) gave, in addition to the N_b-oxide, a compound (14) whose i.r. spectrum showed hydroxy-absorption at 3380 and lactam absorption at 1690 cm^{-1}. Its n.m.r. spectrum showed a hydroxy-proton signal at δ 4·18 and the C-11 proton signals as AB doublets (*J* 16 Hz) at δ 2·54 and 2·38, and lacked the C-10 proton signals at δ *ca.* 3·10. The mass spectrum showed a molecular ion at *m/e* 442, corresponding to the composition $C_{24}H_{30}N_2O_6$ and a fragmentation pattern similar to those of the hydroxy-lactams (8a) and (11a). Refluxing in acetic anhydride–pyridine failed to give the acetate.

In an attempt to prepare the aldehyde (4) from the more abundant cylindrocarine (2a), various methods were tried to degrade the angular methoxycarbonyl group. The reaction of phenylmagnesium bromide with cylindrocarine (2a) under various conditions failed to give the desired diphenylcarbinol or its dehydration product. The main problem appeared to be the insolubility of the Grignard complex with sodium and many attempts were made to overcome it by preparing the Grignard reagent and carrying out the reaction in solvents such as hexamethylphosphoramide,[23a] triethylamine, benzene,[23b] and tetrahydrofuran in addition to diethyl ether, but none was successful. Acetylation of the nitrogen atom did not obviate the problem.

In another approach to avoid the solubility problem, cylindrocarine (2a) was *N*-methylated by formylation with acetic anhydride and formic acid to give the known *N*-formylcylindrocarine [4] followed by reduction with lithium aluminium hydride. Its oxidation with different reagents gave only poor yields of the corresponding acid, which on esterification with diazomethane gave *N*-methylcylindrocarine (2d). A better route to the same compound consisted of *N*-methylation of cylindrocarine (2a) with sodium hydride and methyl iodide.[24]

The resulting *N*-methylcylindrocarine (2d) was treated with phenylmagnesium bromide to give the diphenylcarbinol, which was dehydrated to the olefin (15). This substance was not hydroxylated by osmium tetroxide, and all approaches to convert it to *N*-methylnorcylindrocarpinal, including ozonolysis,[25a] osmium tetroxide–sodium periodate oxidation,[25b] and ruthenium tetroxide–sodium periodate oxidation,[25c] were unsuccessful.

At the same time that these studies were being carried out, a slightly different approach was also being investigated to convert cylindrocarine (2a) into the aldehyde (4). *N*-Acetyl-21-*O*-acetylcylindrocarpinol (13b) was partially hydrolysed to *N*-acetylcylindrocarpinol (13c), which on oxidation gave *N*-acetylcylindrocarpinal (16). Its physical and spectral properties were consistent with the aldehyde structure. Reaction of phenylmagnesium bromide with the aldehyde (16) furnished the phenylcarbinol (17). Its i.r. spectrum lacked carbonyl absorption and showed hydroxy-absorption at 3600 and 3350 cm^{-1}. Its n.m.r. spectrum lacked the singlet at δ 2·20 ($CH_3{\cdot}CO$) and had signals for five additional aromatic protons in the δ 6·7—7·2 region. The mass spectrum established the molecular composition $C_{26}H_{32}N_2O_2$.

Dehydration of the carbinol (17) with pyridine and thionyl chloride [26] gave two products, the major one of which was shown to be the olefin (18a) from its spectral

* This name was suggested previously.[22] We suggest the name cylindrocarpinal for the corresponding aldehyde.

[20] K. S. Brown, jun., H. Budzikiewicz, and C. Djerassi, *Tetrahedron Letters*, 1963, 1731.

[21] H. Achenbach, *Tetrahedron Letters*, 1967, 1793.

[22] B. V. Milborrow and C. Djerassi, *J. Chem. Soc.* (*C*), 1969, 417.

[23] (*a*) H. Normant, *Bull. Soc. chim. France*, 1963, 1888; J. Cuvigny and H. Normant, *ibid.*, 1964, 2000; J. Cuvigny, J. Normant, and H. Normant, *Compt. rend.*, 1964, **258**, 3502; (*b*) E. C. Ashby and R. Reed, *J. Org. Chem.*, 1966, **31**, 971.

[24] A. Jackson, N. D. V. Wilson, A. J. Gaskell, and J. A. Joule, *J. Chem. Soc.* (*C*), 1969, 2738.

[25] (*a*) M. B. Rubin, *J. Chem. Educ.*, 1964, **41**, 388; W. L. Meyer, D. D. Cameron, and W. S. Johnson, *J. Org. Chem.*, 1962, **27**, 1130; W. S. Johnson, J. C. Collins, jun., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartmann, *J. Amer. Chem. Soc.*, 1963, **85**, 1409; P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood, and G. F. Woods, *J. Chem. Soc.*, 1952, 4890; P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lobell, and G. F. Woods, *ibid.*, 1954, 125; (*b*) H. Vorbruggen and C. Djerassi, *Tetrahedron Letters*, 1961, 119; H. Vorbruggen and C. Djerassi, *J. Amer. Chem. Soc.*, 1962, **84**, 2990; D. Dvornik and O. E. Edwards, *Canad. J. Chem.*, 1957, **35**, 860; (*c*) G. Stork, A. Meisels, and J. E. Davies, *J. Amer. Chem. Soc.*, 1963, **85**, 3419; H. Nakata, *Tetrahedron*, 1963, **19**, 1959; F. Sondheimer, R. Mechoulam, and M. Sprecher, *ibid.*, 1964, **20**, 2473.

[26] W. S. Allen and S. Bernstein, *J. Amer. Chem. Soc.*, 1955, **77**, 1028; S. Bernstein, R. Littel, S. M. Stolar, L. I. Feldman, and R. H. Blank, *ibid.*, 1956, **78**, 5693.

properties. The second product had the same molecular composition as olefin (18a), $C_{26}H_{30}N_2O$, but showed a different fragmentation pattern in its mass spectrum. Its n.m.r. spectrum (Figure 5) showed a one-proton quartet (J 4 and 12 Hz) at δ 4·74 (PhC*H*), signals for eight aromatic protons at δ 6·30—7·20, and a two-proton multiplet at δ 3·12 (10-H_2), and the methoxy-signal had moved upfield to δ 2·90 p.p.m. These data,

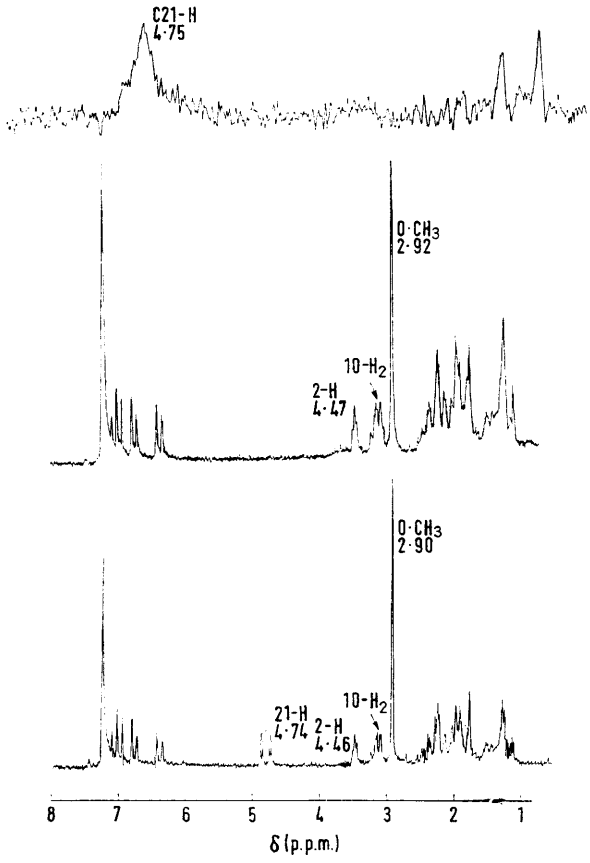


FIGURE 5 N.m.r. spectra of amines (19a), (19b), and (19c)

and the fact that the compound resisted acetylation, suggested structure (19).*

To confirm this assumption, the [21-^{2}H]-carbinol (17d) was prepared: acetylation of the carbinol (17a) gave the diacetate (17b), which was partially hydrolysed to give the *N*-acetyl carbinol (17c) and oxidised to the ketone (20a). This ketone (20a) was hydrolysed to give compound (20b), which was then reduced with lithium aluminium deuteride to give the labelled alcohol (17d). This was treated with pyridine and thionyl chloride, and the products were separated by t.l.c. The labelled analogue (19b) showed the molecular composition $C_{26}H_{29}DN_2O$ (mass spectrometry) and a fragmentation pattern identical with that of (19a) except that the prominent non-indole-containing peaks were shifted by one mass unit. Its n.m.r. spectrum (Figure 5) was identical with that of (19a) except for the one-proton quartet at δ 4·74, which had disappeared.

The phenyl ketone (20b) was treated with deuterium oxide and sodium in [^{2}H]methanol and reduced with lithium aluminium hydride to the [20-$^2H_2$]carbinol (17e); this was converted into compound (19c), which showed a broad singlet at δ 4·75 in its n.m.r. spectrum (Figure 5). Its mass spectrum displayed a molecular ion at *m/e* 388 ($C_{26}H_{28}D_2N_2O$) and a fragmentation pattern with that of (19a), with appropriate 2 mass unit shifts.

Olefin (18a) was acetylated to (18b), and all attempted degradation reactions were carried out with this olefin (18b). Many methods, including ozonolysis, epoxidation, osmylation, and other oxidations were tried to degrade the olefin (18b) to the aldehyde (4) or the corresponding acid but none succeeded.

The oxidation of some *Aspidosperma* alkaloids with *m*-chloroperbenzoic acid thus makes possible functionalisation at C-10 and C-19, which are not easily accessible by other methods. More important, in those compounds which bear an oxo-function at C-20, the method provides a means of degrading the angular ethyl function and of entry into the unsubstituted cyclic skeleton of aspidospermine.

Some of the compounds prepared exhibited interesting mass spectral fragmentation patters. We report some of the deuterium-labelling studies performed with one of them, the phenylcarbinol (17a). The base peak (at 70 eV) appears at *m/e* 269, corresponding to $M - 135$. In the low voltage (15 eV) spectrum the peak at *m/e* 269 is still the second most important peak (62%). The generation of such a peak could be rationalised by the loss of 28 (C_2H_4) and 107 (C_6H_5·ĊH·OH) mass units. However there exists a metastable peak for the transition $M^+ \longrightarrow$ *m/e* 269. The mass spectra (Table) of the labelled compounds (17d) and (17e) show that the C-21 deuterium atom is lost but that at C-20 retained in the *m/e* 269 ion.

Fragmentation pattern of 21-phenylcylindrocarpinol (17a) and deuteriated analogues

	M^+	*m/e*
$C_{26}H_{32}N_2O_2$ (17a)	404	386, 297, 269, 244, 216, 174, 110, 109
$C_{26}H_{31}DN_2O_2$ (17d)	405	387, 297, 269, 245, 217, 174, 110, 109
$C_{26}H_{30}D_2N_2O_2$ (17e)	406	387, 299, 271, 246, 218, 174, 112, 111
$C_{26}H_{30}D_2N_2O_2$ (21a)	406	388, 299, 271, 246, 218, 174, 112, 111
$C_{26}H_{29}D_3N_2O_2$ (21b)	407	389, 299, 271, 247, 219, 176, 112, 111

In order to determine the origin of the other two expelled carbon atoms, the carbinols (21a) and (21b) were prepared. The former was synthesised by oxidation of (17b) with mercury(II) acetate and acetic acid,[12,27] formic [^{2}H]acid reduction of the resulting enamine,[28] and removal of the acetate groups by consecutive treatment with dilute alkali and phenylmagnesium bromide. The alcohol (21b) was prepared

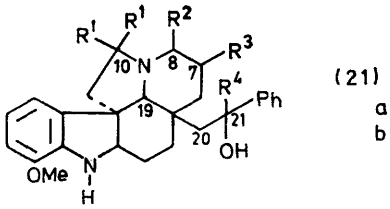
* A molecular model of structure (19) shows that the methyl protons of ring A are established by the other phenyl group; this accounts for their upfield shift to δ 2·90 p.p.m.

[27] N. J. Leonard and F. P. Hauch, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 5279.

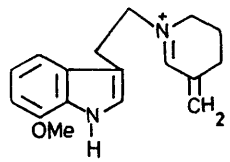
[28] N. J. Leonard and R. R. Sauers, *J. Amer. Chem. Soc.*, 1957, **79**, 6210.

by oxidation of (20a) with chromium trioxide in pyridine, hydrolysis with acid, and reduction with lithium aluminium deuteride.

The mass spectra (Table) of both (21a) and (21b) show that none of the deuterium atoms are lost, thus proving that carbon atoms 7, 8, and 10 must be retained. The only two other carbon atoms that can be expelled are C-3 and C-4; our results agree with previous findings on the fragmentation of *Aspidosperma* alkaloids [11,18] and also with the fact that the presence of a metastable peak does not necessarily indicate a one-step decomposition reaction.[29] The most reasonable structure for the ion of *m/e* 269 is therefore (22).



(21) R¹ R² R³ R⁴
a; H D D H
b; D H H D



(22) *m/e* 269

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Rotations were measured for solutions in chloroform or methanol with a Perkin-Elmer model 141 polarimeter. U.v. spectra were measured for solutions in 95% ethanol with a Cary model 14 spectrophotometer. The mass spectra (70 eV; direct inlet system) were determined by Dr. A. Duffield, Mr. R. Ross, and Mr. C. Carroll with either an Atlas CH-4 or an A.E.I. MS-9 instrument, and high resolution measurements were performed with the latter. The n.m.r. spectra were obtained by Drs. L. Durham and M. Bramwell with a Varian HA-100 or a T-60 spectrometer, with deuteriochloroform as solvent and tetramethylsilane as internal reference. I.r. spectra were determined with either a Perkin-Elmer model 700 Infracord or a model 421 grating spectrophotometer for solutions in chloroform unless otherwise specified. Microanalyses were carried out by Messrs. J. Consul and E. H. Meier. T.l.c. was performed on aluminium oxide GF_{254} (Merck), with single or multiple development; 1 m plates were used for preparative purposes. The spots were detected with cerium(IV) sulphate spray, iodine vapour, or u.v. light. All organic solutions were dried with anhydrous sodium sulphate.

Isolation of Alkaloids.—The ethanolic extract of *A. cylindrocarpon* (437 g) was dissolved in glacial acetic acid (300 ml) and diluted with water (2·7 l). The precipitate was allowed to settle overnight and the solution was filtered through Celite and extracted with methylene chloride (3 × 500 ml). The aqueous layer was neutralized to pH 7 with sodium hydrogen carbonate and extracted with methylene chloride (5 × 500 ml). Evaporation of the methylene chloride under reduced pressure afforded a crude mixture (16 g) which contained mostly *N*-acylated analogues of cylindrocarine (2a) and 20-hydroxycylindrocarine (2b). This was separated into groups of three or more alkaloids by column chromatography on neutral aluminium oxide (Woelm) of activity 3 (benzene–methylene chloride as eluant). The mixtures were separately hydrolysed by refluxing on a steam-bath with 6N-hydrochloric acid under nitrogen for 6 h. The mixture was filtered, the water removed under reduced pressure, and the residue taken up in methanol and treated with ethereal diazomethane. The resulting mixture of alkaloids was purified by preparative t.l.c. on 1 m alumina plates developed in acetone–hexane–water. 20-Hydroxycylindrocarine (2b) (1·5 g) and cylindrocarine (2a) (3·8 g) were obtained in this manner. Cylindrocarine (2a) had m.p. 142—143° (from aqueous methanol) (authentic material 141—142°), $[\alpha]_D^{21}$ −11° (*c* 1·15 in $CHCl_3$); * i.r., u.v., n.m.r., and mass spectra were identical with those of the authentic material.[4] Acetic anhyride–pyridine acetylation provided cylindrocarpidine, m.p. 120—121° (from aqueous ethanol). 20-Hydroxycylindrocarine (2b) had m.p. 87—90° (from acetone–hexane), $[\alpha]_D^{21}$ −84° (*c* 1·17 in $CHCl_3$); i.r., u.v., and mass spectra identical with those of the authentic material,[4] δ 2·74 (1H, d, *J* 6 Hz, OH), 2·93 (1H, s, 19-H), 3·60 (1H, m, 2-H), 3·79 (3H, s, O·CH_3), 3·88 (3H, s, O·CH_3), 4·31 (1H, d, *J* 6 Hz, 20-H), and 6·55—6·93 p.p.m. (3H, m, aromatic).

20-Hydroxycylindrocarpinol (3a).—20-Hydroxycylindrocarine (2b) (520 mg) was dissolved in anhydrous benzene–ether (1 : 5 v/v; 15 ml) and added slowly to ice-cooled lithium aluminium hydride (100 mg) in ether. The mixture was refluxed for 2 h, then cooled and the excess of hydride was decomposed by adding just enough saturated aqueous sodium sulphate. The solution was decanted and the salts were washed with benzene–ether; the combined organic extract was evaporated under reduced pressure; $\nu_{max.}$ ($CHCl_3$), 3600br, 1600w, 1580, 1480s and 1260 cm^{-1}, δ 2·96—3·20 (2H, m, 10-H_2), 3·80 (3H, s, O·CH_3), and 6·40—6·78 p.p.m. (3H, m, aromatic), *m/e* 344 (M^+, 58%), 313(8), 285(100), 184(20), 174 (18), 160(15), and 156(90).

N-Acetyl-20-hydroxycylindrocarpinol (3b).—The crude 20-hydroxycylindrocarpinol (3a) was acetylated with acetic anhydride–pyridine. The product was dissolved in methanol (10 ml) and 10% aqueous sodium hydroxide (5 ml) and warmed (steam-bath) for 40 min. The flask was cooled, water (10 ml) was added, and the mixture was extracted with methylene chloride. The organic extracts were dried and evaporated and the product purified by t.l.c.; $\nu_{max.}$ 3630w, 3400br, 1625s, 1480, and 1260 cm^{-1}, δ 2·20 (3H, s, Ac), 2·39 (1H, s, 19-H), 3·87 (3H, s, O·CH_3), 4·55 (1H, m, 2-H), and 6·65—7·2 p.p.m. (3H, m, aromatic), *m/e* 386 (M^+, 50%), 355(8), 327(100), 325(31), 184(17), 174(13), 160(9), and 156(85).

N-Acetylnorcylindrocarpinal (4).—The alcohol (3b) (300 mg) was dissolved in 95% ethanol (15 ml) and chilled.

* Previously [4] the rotation was reported as −280° (*c* 0·0025 in MeOH). Owing to the small amounts of material available, those rotations were determined from o.r.d. curves and were therefore liable to be inaccurate.

[29] J. Seibl, *Helv. Chim. Acta*, 1967, **50**, 263; H. Budzikiewicz, C. Djerassi, and D. H. Williams, 'Mass Spectrometry of Organic Compounds,' Holden-Day, San Francisco, 1967, pp. 29—30.

Periodic acid crystals (179 mg) were dissolved in distilled water (10 ml) and added slowly with stirring to the cold solution. Stirring was then continued at room temperature; the reaction was complete after 2 h (t.l.c.). The ethanol was removed under reduced pressure and 10% aqueous sodium carbonate (10 ml) was added. The mixture was extracted several times with methylene chloride; the organic extracts were washed with distilled water, dried, and evaporated. The residue was a white crystalline *material* (250 mg, 91%), m.p. 219—220° (from acetone), $[\alpha]_D^{26}$ −97° (*c* 0·913 in MeOH), $\lambda_{max.}$ 218 and 256 nm (log ε 4·59 and 4·11), $\lambda_{sh.}$ 289 nm (log ε 3·57), $\lambda_{min.}$ 237 nm (log ε 3·85), $\nu_{max.}$ 1720s, 1650br, 1445, 1380s, 1320, 1210s, 1120, and 920m cm^{-1}, δ 2·17 (3H, s, Ac), 2·79 (1H, s, 19-H), 3·0—3·34 (2H, m, 10-H_2), 3·82 (3H, s, O·CH_3), 4·57 (1H, q, *J* 6 and 10 Hz, 2-H), 6·74—7·16 (3H, m, aromatic), and 9·28 p.p.m. (1H, s, CHO), *m/e* 354 (M^+, 100%), 326(65), 325(84), 311(25), 283(25), 190(18), 174(11), 160(36), 152(21), 124(60), and 96(57) (Found: C, 71·1; H, 7·35; N, 7·75%; M^+, 354·191. $C_{21}H_{26}N_2O_3$ requires C, 71·15; H, 7·4; N, 7·9%; M^+, 354·194).

Oxidation of Aldehyde (4) *with* m-*Chloroperbenzoic Acid.*—The aldehyde (4) (38 mg) was dissolved in methylene chloride (10 ml) and chilled. Commercial *m*-chloroperbenzoic acid (20 mg) was dissolved in methylene chloride and added slowly with stirring, and the mixture was left overnight at room temperature. Washing twice with saturated sodium hydrogen carbonate, drying, and evaporation gave a highly polar white material (N_b-oxide) (32 mg, 81%), $\nu_{max.}$ 1720s, 1650br, 1485, 1460s, 1380s, 1270 and 940br cm^{-1}, *m/e* 370 (M^+, 34%), 354(12), 342(39), 341(100), 325(37), 324(42), 311(38), 281(14), 212(35), 174(28), 160(43), 156(75), 139(84), and 111(70).

Reduction of the N_b-*Oxide of Aldehyde* (4).[7]—The N_b-oxide (20 mg) was dissolved in methanol (7 ml) and hydrogenated for 2·5 h over Raney nickel W-2 (atmospheric pressure). After filtration and evaporation the residue was purified by t.l.c. and gave two products. The less polar one proved to be the aldehyde (4); the more polar one (5) (see later) had $\nu_{max.}$ 3600w, 3400br, 1620s, 1480, 1450s, and 1385s cm^{-1}, *m/e* 356 (M^+, 100%), 328(34), 325(33), 174(7), 160(8), 154(21), and 126(28).

N-*Acetylnorcylindrocarpinol* (5).—The aldehyde (4) (5 mg) in ethanol (2 ml) was added to sodium borohydride (3 mg) in ethanol (5 ml) and stirred for 1 h. The excess of borohydride was destroyed with aqueous acetic acid, and the solution was made basic with 10% aqueous sodium carbonate and extracted with methylene chloride. Evaporation gave the product, which displayed properties identical (t.l.c., i.r. and mass spectra) with those of the 'more polar' product of the previous experiment.

20-*Hydroxyaspidospermine* (7b).—A solution of the aldehyde (4) (40 mg) in benzene (5 ml) was added to an excess of methylmagnesium iodide in ether at 0°. The mixture was refluxed for 30 min and then stirred for 2 h at room temperature. The flask was cooled, the excess of Grignard reagent was decomposed with saturated ammonium chloride solution and the organic layer was decanted. The salts were washed with benzene and the combined solution was evaporated. T.l.c. gave two products. The less polar (7a) (8 mg, 21%) gave a violet colour with cerium(IV) sulphate reagent, characteristic of the *N*-deacyl members of the cylindrocarine series. It was acetylated with acetic anhydride–pyridine and the product partially hydrolysed with methanolic sodium hydroxide to give (7b), identical with the more polar material (25 mg, 60%); m.p. 200—201° (from acetone), $\nu_{max.}$ 3620w, 1625m, 1510, 1480, 1390, 1205s, and 1050 cm^{-1}, *m/e* 370 (M^+, 100%), 342(53), 325(74), 174(9), 168(27), 160(10) and 140(49).

20-*Oxoaspidospermine* (6).—The alcohol (7b) (250 mg) in dimethyl sulphoxide (1·9 ml) was stirred with orthophosphoric acid (10M-solution in Me_2SO; 0·1 ml) and dicyclohexylcarbodi-imide (633 mg). After 18 h at room temperature the mixture was worked up following the modified procedure of Albright and Goldman;[9] t.l.c. screening showed that most of the alkaloid appeared in the first methylene chloride extract of the reaction mixture. This was evaporated and the residue taken up in acetic acid–water (1 : 2 v/v); the solution was filtered and chilled, made alkaline with ammonia, and extracted with methylene chloride. The *product*, purified by t.l.c. (yield 162 mg, 65%) had m.p. 206—207° (from acetone), $[\alpha]_D^{27}$ −76° (*c* 0·985 in MeOH), $\lambda_{max.}$ 217 and 256 nm (log ε 4·92 and 4·53), $\lambda_{min.}$ 237 nm (log ε 4·28), $\nu_{max.}$ 1695, 1625s, 1480, 1450s, and 1380s cm^{-1}, δ 1·95 (3H, s, Ac), 2·15 (3H, s, Ac), 3·00—3·32 (3H, m, 19-H and 10-H_2), 3·81 (3H, s, O·CH_3), 4·57 (1H, q, *J* 6 and 10 Hz, 2-H), and 6·7—7·2 p.p.m. (3H, m, aromatic), *m/e* 368 (M^+, 47%), 353(6), 325(100), 310(8), 283(5), 174(2), 166(3), 160(6), and 138(13) (Found: C, 71·8; H, 7·7; N, 7·4. $C_{22}H_{28}N_2O_3$ requires C, 71·7; H, 7·65; N, 7·6%).

Oxidation of the Ketone (6) *with* m-*Chloroperbenzoic Acid.**—Ketone (6) (32 mg) was dissolved in dry methylene chloride (15 ml) and chilled. Commercial *m*-chloroperbenzoic acid (excess) was dissolved in dry methylene chloride and added slowly with stirring at 0°. The flask was protected with a calcium chloride tube and stirring was continued for 4 h. The mixture was left overnight at room temperature in the dark, then evaporated under reduced pressure; saturated sodium hydrogen carbonate solution was added and the mixture was extracted with methylene chloride. The extract was dried and evaporated; the residue afforded two main products, the hydroxy-keto-lactam (8a) (6·2 mg, 18%) and the N_b-oxide. The N_b-oxide was warmed on a steam-bath with aqueous 5% iron(II) sulphate[15] and extracted with methylene chloride. Purification of the product gave ketone (6). 19-*Hydroxy*-10,20-*dioxoaspidospermine* (8a) crystallized from acetone–hexane with m.p. 236—237°, $[\alpha]_D^{20}$ +17° (*c* 1·10 in $CHCl_3$), $\lambda_{max.}$ 217, 254, and 287 nm (log ε 4·45, 3·93, and 2·40), $\lambda_{min.}$ 237 and 2·77 nm (log ε 3·65 and 2·30), $\nu_{max.}$ 3380, 1710sh, 1690s, 1640, 1485, 1450, and 1380s cm^{-1} (for n.m.r. see Figure 1), *m/e* 398 (M^+, 100%), 356(96), 338(8), 295(29), 187(27), 186(26), 174(22), 160(60), 145(19), 130(10), and 120(11) (Found: C, 66·2; H, 6·6; N, 6·95%; M^+, 398·175. $C_{22}H_{26}N_2O_5$ requires C, 66·35; H, 6·6; N, 7·05%; M^+, 398·184).

10,20-*Dioxoaspidospermine* (8b).—The ketone (6) (20 mg) in dry pyridine (2 ml) was added to a solution of chromium trioxide (80 mg) in pyridine (5 ml) and stirred for 5 h. The solution was put on a small column of neutral alumina and eluted with methylene chloride. The eluate was evaporated and the residue was purified by t.l.c.; the major product had m.p. 266—268° (from acetone), $\nu_{max.}$ 1700sh, 1690s, 1590, 1485s, 1460s, and 1380s cm^{-1}, δ 2·00 (3H, s, Ac), 2·18 (3H, s, Ac), 2·4 (2H, m, 11-H_2), 3·82 (3H, s, O·CH_3),

* Other procedures included oxidation at room temperature for from 1 to 5 days. The same products were obtained with little variation in the yields.

4·5 (1H, m, 2-H), and 6·7—7·2 p.p.m. (3H, m, aromatic), *m/e* 382 (M^+, 100%), 340(76), 339(51), 298(86), 218(13), 176(32), 174(12), 160(26), 122(23), and 96(20).

Conversion of the Hydroxy-keto-lactam (8a) *into the Enamide* (9a).—The lactam (8a) (100 mg) was dissolved in acetic anhydride (2 ml) and one small drop of concentrated sulphuric acid was added, whereupon the solution turned yellow. It was warmed on a steam-bath for 30 min, then cooled, made alkaline with aqueous 10% sodium hydroxide, and extracted with methylene chloride. Drying and evaporation gave material which was purified by t.l.c. and gave white crystalline 5-*de-ethyl*-10-*oxo*-$\Delta^{5(19)}$-*aspidospermine* (9a) (51 mg, 60%), m.p. 240—242° (from acetone), $[\alpha]_D^{22}$ −232° (*c* 0·861 in $CHCl_3$), $\lambda_{max.}$ 216 nm (log ε 4·54), $\lambda_{sh.}$ 255 and 290 nm (log ε 4·20 and 3·60), $\nu_{max.}$ 1690s, 1630, 1480, 1450, 1380, and 1200s cm^{-1} (for n.m.r. spectrum see Figure 2), *m/e* 338 (M^+, 100%), 319(32), 305(25), 296(47), 295(86), 280(25), 253(22), 174(26), 160(7), and 120(64) (Found: C, 71·0; H, 6·6; N, 8·1%; M^+, 338·164. $C_{20}H_{22}N_2O_3$ requires C, 71·0; H, 6·55; N, 8·3%; M^+, 338·163).

Hydrolysis of the Enamide (9a).—The enamide (9a) (70 mg) was dissolved in methanol (15 ml) and aqueous 10% sodium hydroxide (6 ml) and refluxed (steam-bath) for 8 h. After cooling, water was added and the mixture was extracted with methylene chloride. Evaporation left white crystalline N-*deacetyl*-5-*de-ethyl*-10-*oxo*-$\Delta^{5(19)}$-*aspidospermine* (9b) (55 mg, 90%), m.p. 187—188° (from acetone), $\nu_{max.}$ 1680s, 1490, 1460, and 1410 cm^{-1}, δ 2·62 (2H, s, 11-H_2), 3·46 (1H, m, 2-H), 3·83 (3H, s, O·CH_3), and 6·60—6·74 p.p.m. (3H, m, aromatic), *m/e* 296 (M^+, 89%), 268(7), 253(15), 200(8), 174(20), 160(4), and 120(100) (Found: M^+, 296·148. $C_{18}H_{20}N_2O_2$ requires M^+, 296·152).

N-*Deacetyl*-5-*de-ethylaspidospermine* (10).—The enamide (9b) (28 mg) was dissolved in dry tetrahydrofuran (10 ml) and introduced into 1M-diborane in tetrahydrofuran (0·15 ml; commercial) at 0°. The mixture was refluxed for 1 h under nitrogen and cooled to room temperature; 3M-hydrochloric acid (5 ml) was then added. The mixture was refluxed again for 20 min, cooled, made alkaline with saturated sodium hydrogen carbonate solution, and extracted with methylene chloride. T.l.c. afforded four products which had the same mass spectra and presumably were the four possible stereoisomers corresponding to (10). The major *product* (10) (30% yield) crystallized from acetone–hexane; m.p. 112—113°, $[\alpha]_D^{21}$ +58° (*c* 0·63 in $CHCl_3$), $\lambda_{max.}$ 211, 242, and 287 nm (log ε 4·04, 3·30, and 3·20), $\lambda_{min.}$ 236 and 264 nm (log ε 3·28 and 2·83), $\nu_{max.}$ 3360w, 1610, 1575, 1480, 1450, 1260s, 1170, 1045s, and 925 cm^{-1} (for n.m.r. and mass spectra see Figures 4 and 3) (Found: M^+, 284·183. $C_{18}H_{24}N_2O$ requires M^+, 284·189).

19-*Hydroxy*-10-*oxocylindrocarpidine* (11a).—Cylindrocarpidine (2c) (150 mg) was oxidised with *m*-chloroperbenzoic acid in the same way as ketone (6). Purification gave a crystalline product (24 mg, 15%), m.p. 239—240° (from acetone), $[\alpha]_D^{25}$ −91° (*c* 0·722 in $CHCl_3$), $\lambda_{max.}$ 217, 248, and 288 nm (log ε 4·62, 4·11, and 3·69), $\lambda_{min.}$ 236 and 276 nm (log ε 3·81 and 3·54), $\nu_{max.}$ 3290, 1735, 1700s, 1615, 1490, 1460, 1380, and 1270 cm^{-1}, δ 2·14 (3H, s, Ac), 2·19 and 2·59 (2H, AB doublets, *J* 16 Hz, 20-H_2), 2·38 and 2·60 (2H, AB doublets, *J* 16 Hz, 11-H_2), 3·0 (1H, m, 8-H_{ax}), 3·60 (3H, s, CO_2·CH_3), 3·85 (3H, s, O·CH_3), 3·84 (1H, m, 8-H_{eq}), 4·34 (1H, m, 2-H), 5·64 (1H, s, OH), and 6·80—7·62 p.p.m. (3H, m, aromatic), *m/e* 428 (M^+, 90%), 397(13), 386(100), 354(21), 295(10), 188(12), 174(19), and 160(35).

10-*Oxocylindrocarpidine* (11b).—Cylindrocarpidine (2c) (56 mg) was oxidized with chromium trioxide (122 mg) in dry pyridine (10 ml) in the same manner as ketone (6). After t.l.c. the major product was crystallized from di-isopropyl ether (yield 11 mg, 19%), m.p. 217—218° (lit.,[21] 213°), $[\alpha]_D^{20}$ −64° (*c* 0·38 in $CHCl_3$), $\lambda_{max.}$ 218, 255, and 284 nm (log ε 4·51, 4·00, and 3·51), $\lambda_{min.}$ 235 and 277 nm (log ε 3·35 and 3·30), $\nu_{max.}$ 1730, 1680s, 1635, 1490, 1460, and 1380 cm^{-1}, δ 2·17 (3H, s, Ac), 2·23 and 2·53 (2H, AB doublets, *J* 16 Hz, 11-H_2), 3·68 (3H, s, CO_2·CH_3), 3·86 (3H, s, O·CH_3), 4·04 (1H, s, 19-H), 4·48 (1H, m, 2-H), and 6·82—7·20 p.p.m. (3H, m, aromatic), *m/e* 412 (M^+, 78%), 370(100), 339(12), 338(9), 296(15), 174(10), 160(19), and 120(23).

N-*Deformyl*-N-*acetyl*-10-*oxodichotamine* (12a).—The hydroxy-lactam (11a) (8 mg) was heated on a steam-bath for 24 h with acetic anhydride (1 ml) and pyridine (2 ml). The solution was evaporated under reduced pressure and the product purified by t.l.c.; $\nu_{max.}$ 1770s, 1700s, 1640, 1480, 1450, 1380s, and 1185 cm^{-1}, δ 2·15 (3H, s, Ac), 2·06 and 2·40 (2H, AB doublets, *J* 16 Hz, 20-H_2), 2·55 (2H, s, 11-H_2), 2·90 (1H, m, 8-H_{ax}), 3·86 (3H, s, OCH_3), 4·14 (1H, m, 8-H_{eq}), 4·46 (1H, m, 2-H), and 6·84—7·30 p.p.m. (3H, m, aromatic), *m/e* 396 (M^+, 67%), 354(100), 174(16), and 160(11).

The same compound was obtained by acetylation and oxidation with chromium trioxide in pyridine[12] of *N*-deformyldichotamine (12b).[20]

Cylindrocarpinol (13a).—Cylindrocarine (2a) (300 mg) was reduced with lithium aluminium hydride (60 mg) in in the same way as 20-hydroxycylindrocarine (2b). The product (260 mg, 94%) gave white needles, m.p. 149—150° (from di-isopropyl ether), $\nu_{max.}$ 3610, 3380, 1620, 1600, 1490, 1460, and 1270 cm^{-1}, *m/e* 328 (M^+, 20%), 310(4), 300(8), 269(7), 174(4), 168(6), 160(4), and 140(100).

N-*Acetyl*-21-O-*acetylcylindrocarpinol* (13b).—Cylindrocarpinol (13a) (150 mg) was acetylated with acetic anhydride–pyridine and gave white needles, m.p. 214—215° (from di-isopropyl ether), $\nu_{max.}$ 1730, 1630s, 1485, 1460, 1380, and 1240br cm^{-1}, δ 1·91 (3H, s, Ac), 2·17 (3H, s, Ac), 2·98—3·22 (2H, m, 10-H_2), 3·86 (3H, s, O·CH_3), 3·90—4·12 (2H, m, 21-H_2), 4·52 (1H, m, 2-H), and 6·75—7·14 p.p.m. (3H, m, aromatic), *m/e* 412 (M^+, 31%), 384(9), 324(24), 210(8), 182(100), 174(7), 160(5), 138(13), and 122(14).

Oxidation of the Acetate (13b) *with* m-*Chloroperbenzoic Acid*.—The acetate (13b) (100 mg) was oxidized with *m*-chloroperbenzoic acid in the same manner as ketone (6). The hydroxy-lactam (14) (21·4 mg, 20%) crystallized from acetone–hexane; m.p. 222—223°, $\nu_{max.}$ 3400, 1730, 1690s, 1635, 1490, 1460, 1380, and 1210 cm^{-1}, δ 1·94 (3H, s, Ac), 2·14 (3H, s, Ac), 2·38 and 2·54 (2H, AB doublets, *J* 16 Hz, 11-H_2), 2·94 (1H, m, 8-H_{ax}), 3·86 (3H, s, O·CH_3), 3·90—4·10 (2H, m, 21-H_2), 4·18 (1H, s, OH), 4·28 (1H, m, 2-H), and 6·81—7·60 p.p.m. (3H, m, aromatic), *m/e* 442 (M^+, 84%), 400(100), 382(24), 340(34), 295(8), 174(18), and 160(46).

Methylation[24] *of Cylindrocarine* (2a).—Cylindrocarine (2a) (50 mg) was dissolved in dry dimethyl sulphoxide (3 ml) and sodium hydride (57% dispersion in oil; 10 mg) was added under nitrogen. The mixture was stirred for a few min, heated for 5 min at 60°, and cooled to room temperature. Methyl iodide (30 mg) in dimethyl sulphoxide (0·3 ml) was added slowly and the mixture was stirred for 1 h, diluted with water (10 ml), and extracted several times with methylene chloride. The *N*-methylcylindro-

carine (2d) obtained in 40% yield had i.r., n.m.r., and mass spectra identical with those of authentic material.[4]

Conversion of N-*Methylcylindrocarine* (2d) *into Olefin* (15).—*N*-Methylcylindrocarine (2d) (300 mg) was added to phenylmagnesium bromide (excess) in ether–benzene (95 : 5 v/v) at 0°; the mixture was refluxed for 2 h and then left overnight at room temperature. The excess of Grignard reagent was decomposed with saturated ammonium chloride solution, the salts were washed with benzene, and the combined organic extracts were evaporated. The crude product was then heated for 3 h (steam-bath) with 3N-hydrochloric acid (15 ml). The solution was cooled and extracted with hexane; the aqueous layer was made alkaline with saturated sodium hydrogen carbonate solution and the mixture was extracted with methylene chloride. After purification by t.l.c., the olefin (15) crystallized from acetone; m.p. 184—186°, $[\alpha]_D^{28}$ −248° (*c* 0·014 in $CHCl_3$), $\nu_{max.}$ 204, 218, and 256 (log ε 3·56, 3·45, and 3·08), $\lambda_{min.}$ 216 and 242 (log ε 3·44 and 3·03), $\nu_{max.}$ 1600sh, 1590, 1485s, 1445, 1350, and 1220br cm^{-1}, δ 2·46 (1H, s, 19-H), 3·01 (3H, s, N·CH_3), 3·73 (3H, s, O·CH_3), 6·05 (1H, s, 20-H), and 6·45—7·27 p.p.m. (13H, m, aromatic), *m/e* 476 (M^+, 100%), 448(32), 400(5), 302(9), 296(17), 283(13), 274(100), 202(20), 188(22), 174(16), 167(22), 160(4), 148(18), 124(34), 109(28), 105(27), and 91(18).

N-*Acetylcylindrocarpinal* (16).—*N*-Acetylcylindrocarpinol (13c) (500 mg), obtained by alkaline hydrolysis of (13b), was oxidized with dimethyl sulphoxide (4 ml), orthophosphoric acid (10M-solution in Me_2SO; 0·2 ml), and dicyclohexylcarbodi-imide (1·7 g).[9] The aldehyde (16) crystallized from acetone (yield 323 mg, 65%); m.p. 206—207°, $\nu_{max.}$ 1720, 1635, 1490, 1460, 1385, and 1215 cm^{-1}, δ 2·20 (3H, s, Ac), 2·44 (1H, s, 19-H), 2·95—3·20 (2H, m, 10-H_2), 3·88 (3H, s, O·CH_3), 4·55 (1H, m, 2-H), 6·72—7·18 (3H, m, aromatic), and 9·71 p.p.m. (1H, t, *J* 3 Hz, CHO), *m/e* 368 (M^+, 12%), 340(5), 324(100), 311(14), 281(12), 174(14), 166(14), 160(11), 138(78), 110(23), and 109(11).

21-*Phenylcylindrocarpinol* (17a).—The aldehyde (16) (250 mg) was added to phenylmagnesium bromide (excess) in ether–benzene (95 : 5 v/v) at 0°; the mixture was refluxed for 2 h and then left overnight at room temperarure. After work-up the product (245 mg, 71%) was purified by t.l.c.; $\nu_{max.}$ 3600, 3350, 1610, 1590, 1490s, 1450, and 1265s cm^{-1}, δ 2·26 (1H, s, 19-H), 2·94—3·20 (2H, m, 10-H_2), 3·82 (3H, s, O·CH_3), 4·70 (1H, m, 21-H), and 6·7—7·2 p.p.m. (8H, m, aromatic), *m/e* 404 (M^+, 43%), 386(2), 269(100), 244(4), 216(9), 174(22), 160(5), 110(8), and 109(7).

Dehydration of the Carbinol (17a).—The carbinol (17a) (39 mg) was dissolved in dry pyridine (10 ml) and cooled in ice–salt. Thionyl chloride (0·4 ml) was added slowly with stirring.[26] The mixture was left overnight at 0°; it was poured into ice–water and the resulting mixture was extracted with methylene chloride. The extract was washed with distilled water, dried, and evaporated. T.l.c. gave two products, the olefin (18a) (13 mg, 35%) and the amine (19a) (5·6 mg, 15%).

The olefin (18a) crystallized from acetone; m.p. 147—148·5°, $\nu_{max.}$ 1660sh, 1615, 1590s, 1485s, 1450, 1390, 1325, 1265, 1220br, 1180, and 1085 cm^{-1}, δ 2·42 (1H, s, 19-H), 2·90—3·25 (2H, m, 10-H_2), 3·55 (1H, m, 2-H), 3·80 (3H, s, O·CH_3), 6·26 (2H, q, *J* 17 and 22 Hz, CH=CHPh), and 6·60—7·20 p.p.m. (8H, m, aromatic), *m/e* 386 (M^+, 100%), 358(12), 282(25), 226(10), 198(57), 174(9), 141(17), 109(13), and 91(10).

The amine (19a) had m.p. 153—154° (from acetone), $\nu_{max.}$ 1590, 1480s, 1450s, 1290, 1270s, 1180, 1130, 1055, and 980 cm^{-1} (for n.m.r. spectrum see Figure 5), *m/e* 386 (M^+, 100%), 358(3), 295(15), 282(9), 267(7), 226(4), 198(10), 193(17), 174(3), 160(6), 110(8), 109(5), and 91(7).

The Phenyl Ketone (20a).—The alcohol (17a) (400 mg) was acetylated with pyridine–acetic anhydride and the product partially hydrolysed with aqueous methanolic sodium hydroxide to the *N*-acetyl derivative (17b). This alcohol (17b) was oxidized at 0° with Jones reagent[30] to the ketone (20a) (308 mg, 70%), $\nu_{max.}$ 1690, 1620br, 1485, 1450, 1385s, 1280, and 1220br cm^{-1}, δ 2·17 (3H, s, Ac), 2·44 and 2·92 (2H, AB doublets, *J* 16 Hz, 20-H_2), 2·62 (1H, s, 19-H), 3·06—3·28 (2H, m, 10-H_2), 3·83 (3H, s, O·CH_3), 4·56 (1H, m, 2-H), and 6·75—7·62 p.p.m. (8H, m, aromatic), *m/e* 443 (M^+ − 1, 1%), 324(100), 281(11), 266(7), 212(2), 174(6), 160(5), and 105(7).

The [21-$^2H_1$]*Amine* (19b).—The phenyl ketone (20b) (27 mg) was hydrolysed by heating (steam-bath) with hydrochloric acid (6N; 3 ml) for 3 h. After work-up, the resulting *N*-deacetyl ketone (20b) was reduced with lithium aluminium deuteride (5 mg) to the [21-^{2}H]phenylcarbinol (17d) (99% ^2H by mass spec.). The labelled alcohol (17d) was treated with thionyl chloride (0·3 ml) in dry pyridine (10 ml) at 0°. Work-up and t.l.c. gave the amine (19b), which showed an i.r. spectrum identical with that of (19a); for n.m.r. spectrum see Figure 5; *m/e* 387 (M^+, 100%), 359(3), 295(13), 282(9), 199(12), 174(4), 160(6) 110(8), and 92(6).

The [20-$^2H_2$]*Amine* (19c).—The phenyl ketone (20b) (15 mg) was refluxed with methan[^{2}H]ol (1·5 ml), deuterium oxide (0·5 ml), and sodium (50 mg) for 10 min. The solution was quickly extracted with methylene chloride after cooling and adding deuterium oxide (1 ml). Evaporation left a residue which was reduced in ether solution with lithium aluminium hydride (5 mg), and the resulting labelled alcohol (17e) (97% $^2H_2$ by mass spec.) was treated with thionyl chloride (0·15 ml) in dry pyridine (5 ml). The [20-$^2H_2$]amine (19c) obtained showed an i.r. spectrum identical with that of the amine (19a); for n.m.r. spectrum see Figure 5; *m/e* 388 (M^+, 100%), 360(3), 297(13), 284(9), 200(10), 174(4), 160(6), 112(8), and 91(5).

21-*Phenyl*[7,8-$^2H_2$]*cylindrocarpinol* (21a).—The acetate (17b) (75 mg) and mercury(II) acetate[27] (250 mg) in acetic acid (5% aqueous solution; 30 ml) were refluxed for 3 h. The solution was cooled. Aqueous sodium sulphide solution was added and the precipitate was filtered off and washed with 5% acetic acid. The combined filtrate and washings were made alkaline with potassium carbonate and extracted with methylene chloride. The enamine so obtained was reduced with formic [^{2}H]acid[28] (2 ml) by heating on a steam-bath for 3 h. The solution was cooled, made alkaline with saturated sodium hydrogen carbonate, and extracted with methylene chloride. The extract was evaporated and the residue was warmed (steam-bath) with aqueous 5% sodium hydroxide (3 ml) and methanol (7 ml) for 30 min. Water (5 ml) was added and the mixture was extracted with methylene chloride. The extract was evaporated and the residue was treated with phenylmagnesium bromide (2 equiv.) in ether–benzene for 30 min at room temperature. Work-up and purification gave the alcohol (21a), $^2H_2$ 49%, $^2H_1$ 15%; *m/e* 406 (M^+, 38%),

[30] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J, *Chem. Soc.*, 1946, 39.

388(2), 284(9), 271(100), 218(6), 174(49), 160(9), 112(6), and 111(9).

21-*Phenyl*[10,21-$^2H_3$]*cylindrocarpinol* (21b).—The ketone (20a) (30 mg) was oxidised with chromium trioxide (80 mg) in pyridine (5 ml). The resulting 10-oxo-compound was purified by t.l.c. and hydrolysed with 6N-hydrochloric acid (5 ml). Reduction of the hydrolysis product with lithium aluminium deuteride (4 mg) in ether afforded the alcohol (21b), $^2H_3$ 73%, *m/e* 407 (M^+, 29%), 389(3), 284(6), 271(100), 242(21), 241(21), 219(9), 176(28), 160(8), 112(9), and 111(10).

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