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Alkaloids of *Darlingia darlingiana*

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Abstract

The structures of eleven alkaloids isolated from *Darlingia darlingiana* (F. Muell.) L. A. S. Johnson, a Queensland proteaceous tree, have been determined. They comprise a tropene, two pyranotropanes, and eight pyrrolidine alkaloids.

Darlingia darlingiana (F. Muell.) L. A. S. Johnson is a tall tree which grows in rain-forest areas of northern Queensland. During a survey of Queensland plants for alkaloids, this species (under the name of *D. spectatissima* F. Muell.) was recorded as giving a positive test,[1] and it appears to be the first proteaceous plant in which alkaloids were detected. Since then, alkaloids have been isolated from this[2] and from several other proteaceous species[3] including the closely related *D. ferruginea* J. F. Bailey.[4] This report describes the isolation of 11 alkaloids from *D. darlingiana* and a study of their structures.

The plant material, extracted by standard methods, yielded about 0·22% of crude alkaloids. The mixture was separated into fractions of different basicities by Craig countercurrent distribution between chloroform and dilute sulfuric acid. After purification by p.t.l.c., a range of bases belonging to three broad structural types was isolated. The major alkaloid, darlingine,* proved to be a pyranotropane base of the bellendine (1)[5] type; its partially reduced analogue, 5,11-dihydrodarlingine, was also isolated in small amount. The only tropane alkaloid present, ferruginine, had previously been found in *D. ferruginea*.[6] The majority of the alkaloids of

* Traditional alkaloid nomenclature has been followed in this paper. The systematic name of tropane is 8-methyl-8-azabicyclo[3,2,1]octane, that of darlingine is 2,3,10-trimethyl-6,7,8,9-tetrahydrocyclohepta[*b*]pyran-5,8-imin-4(5*H*)-one, and that of naturally occurring darlingianine is (2*S*,2′*R*)-1-(1′-methylpyrrolidin-2′-yl)-6-phenylhexa-3,5-dien-2-ol.

[1] Webb, L. J., 'An Australian Phytochemical Survey', Part II, CSIRO Bulletin No. 268, Melbourne, 1952.
[2] Anderson, B. F., Robertson, G. B., Bick, I. R. C., Gillard, J. W., and Leow, H.-M., *Chem. Ind. (London)*, 1977, 764.
[3] Bick, I. R. C., and Leow, H.-M., *J. Indian Chem. Soc.*, special issue in honour of Professor Chatterjee, in press.
[4] Bick, I. R. C., Gillard, J. W., and Woodruff, M., *Chem. Ind. (London)*, 1975, 794.
[5] Motherwell, W. D. S., Isaacs, N. W., Kennard, O., Bick, I. R. C., Bremner, J. B., and Gillard, J. W., *Chem. Commun.*, 1971, 133.
[6] Bick, I. R. C., Gillard, J. W., and Leow, H.-M., *Aust. J. Chem.*, 1979, **32**, 2537.

D. darlingiana belong to the pyrrolidine group with a side chain of varying length terminating in a phenyl group.

Pyranotropane Bases

Darlingine

The molecular formula of darlingine showed it was a higher homologue of bellendine (1)[5] and isobellendine (2),[7] two pyranotropane alkaloids from the Tasmanian proteaceous plant *Bellendena montana* R. Br. which differ from one another only in the position of the *C*-methyl group. The u.v. spectra of all three alkaloids were nearly identical, and the ^{1}H n.m.r. spectra were also similar, the main difference being that darlingine showed no olefinic proton resonance, but had an extra *C*-methyl proton signal instead. The two singlets due to the *C*-methyl groups appeared at nearly the same chemical shifts as those of bellendine and isobellendine. The mass spectrum of darlingine showed a molecular ion and a base peak (5) homologous with those of the other two bases, but fragments resulting from loss or cleavage of the pyranone ring were common to all three. The structure (3) suggested by these data for darlingine was finally proved by a synthesis of the racemic base which followed the same lines as those of bellendine[8] and isobellendine.[7] The absolute stereochemistry of these bases has not yet been determined, and structures (1), (2), and (3) represent relative configurations.

5,11-Dihydrodarlingine

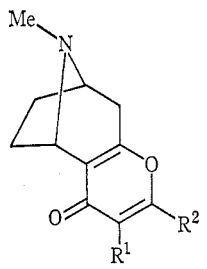
This base has a molecular formula with two extra hydrogens as compared with that of darlingine. Its u.v. spectrum suggested that it had a dihydropyran-4-one chromophore. The two extra hydrogens in the pyran-4-one ring must be located at positions 5 and 11, since the ^{1}H n.m.r. spectrum showed the presence of two methyl groups attached to olefinic carbons. Structure (4) indicated by these observations was supported by the mass spectrum, which showed a general similarity to those of the pyranotropanes; however, 5,11-dihydrodarlingine formed only a weak peak corresponding to the intense pyranopyridinium ion (5), which arises from the loss of the ethano bridge. The base peak was produced instead by loss of the dihydropyranone residue and formation of the ion (6).

The ^{1}H n.m.r. spectrum showed two extra aliphatic proton signals corresponding to H 5 and H 11 as compared to the spectrum of darlingine, but, owing to the small amount of material available, the couplings of these protons with one another and with the neighbouring protons were insufficiently well defined to permit an unequivocal assignment of the stereochemistry at the ring junction.

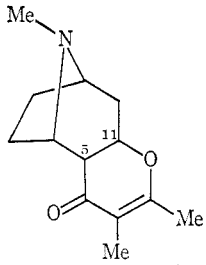
Ferruginine

This alkaloid was shown by spectroscopic methods to be 2-acetyltrop-2-ene (7), and the structure has been confirmed by a synthesis of the enantiomeric base, which established the absolute stereochemistry. Details of this work has been described in a communication dealing with the alkaloids of *D. ferruginea*.[6]

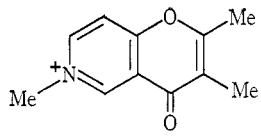
[7] Bick, I. R. C., Gillard, J. W., and Leow, H.-M., *Aust. J. Chem.*, 1979, **32**, 1827.
[8] Bick, I. R. C., Bremner, J. B., and Gillard, J. W., *Tetrahedron Lett.*, 1973, 5099.



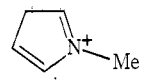
	R^1	R^2	
(1)	Me	H	bellendine
(2)	H	Me	isobellendine
(3)	Me	Me	darlingine



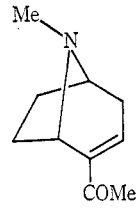
(4) 5,11-dihydrodarlingine



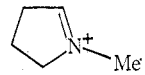
(5) *m/z* 190



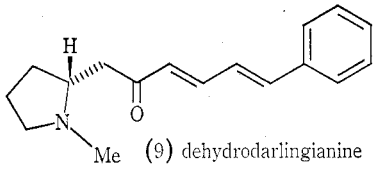
(6) *m/z* 82



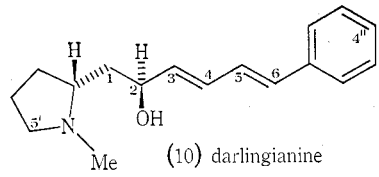
(7) ferruginine



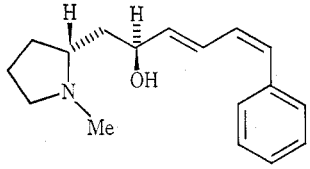
(8) *m/z* 84



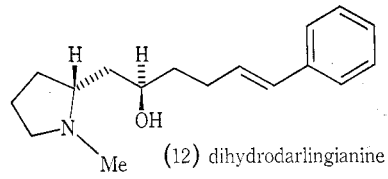
(9) dehydrodarlingianine



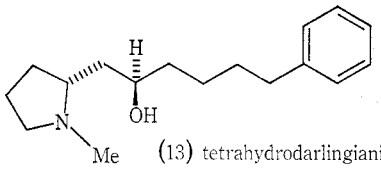
(10) darlingianine



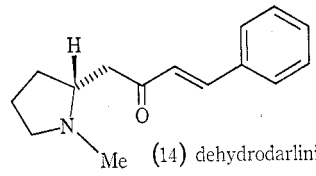
(11) isodarlingianine



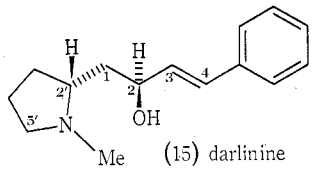
(12) dihydrodarlingianine



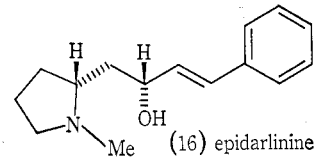
(13) tetrahydrodarlingianine



(14) dehydrodarlinine



(15) darlinine



(16) epidarlinine

C_{17} Pyrrolidine Bases

Dehydrodarlingianine

The yellow base dehydrodarlingianine has a strong u.v. absorption at λ_{max} 322 nm, which indicates a highly conjugated chromophore; its i.r. spectrum gave evidence of a conjugated carbonyl group, a monosubstituted benzene ring, and at least one (*E*)-substituted double bond. These deductions were supported by the ^{1}H n.m.r.

spectrum of dehydrodarlingianine, which also revealed the presence of an *N*-methyl group. The mass spectrum showed several strong nitrogen-containing peaks, including the base peak at *m/z* 84, whose composition suggested the *N*-methyl-1-pyrrolinium structure (8) and a 2-substituted *N*-methylpyrrolidine nucleus for dehydrodarlingianine.

The model compound 6-phenylhexa-3,5-dien-2-one was synthesized for comparison purposes; its u.v. spectrum was practically identical with that of dehydrodarlingianine, and there were also close similarities in those regions of the i.r. and ^{1}H n.m.r. spectra where aromatic and olefinic absorptions occur. The evidence suggested the structure (9) with two (*E*)-substituted double bonds for dehydrodarlingianine, which has been confirmed by a synthesis of the racemic base by condensation of hygrine [1-(1′-methylpyrrolidin-2′-yl)propan-2-one] with cinnamaldehyde.

Darlingianine

The abovementioned model compound, 6-phenylhexa-3,5-dien-2-one, on reduction with borohydride gave a product whose u.v. spectrum was nearly identical with that of darlingianine, the main pyrrolidine base present in the plant. Reduction of dehydrodarlingianine in the same way afforded two epimeric alcohols, one of which gave spectra identical with those of darlingianine. This base is thus represented by a structure of the type (10), which is in accord with all the spectroscopic evidence, including ^{13}C n.m.r. data. The structure was confirmed and the relative stereochemistry was established as shown in (10) by X-ray crystallographic analysis.[2] The absolute stereochemistry is not yet known, but the enantiomeric configurations to naturally occurring (−)-hygroline[9] [(2*S*,2′*S*)-1-(1′-methylpyrrolidin-2′-yl)propan-2-ol] and the diastereomeric (−)-pseudohygroline[9] have been provisionally assigned to the dextrorotary darlingianine and its abovementioned epimer respectively from a comparison of their specific rotations. The configurations of the other pyrrolidine bases from *D. darlingiana* can be correlated with that of darlingianine; further work designed to fix their absolute stereochemistry is in progress.

Isodarlingianine

This isomer of darlingianine was obtained from a fraction in which the two bases occurred together. They had similar properties and spectra, but there were some significant differences. In the ^{1}H n.m.r. spectra of both alkaloids, the olefinic region shows a pair of (*E*)-coupled protons (H 4 and H 3); the latter is also coupled in each case to a proton which from its chemical shift is attached to a carbon bearing a hydroxy group. Darlingianine shows an additional pair of (*E*)-coupled protons (H 5 and H 6), but, in the case of isodarlingianine, the corresponding protons produce a multiplet in which no large coupling can be distinguished. Evidently there is a (*Z*) coupling between these protons, and this conclusion is supported by the u.v. spectrum of isodarlingianine, which shows an absorption maximum at slightly shorter wavelength and of lower intensity as compared with that of darlingianine. That isodarlingianine is an (*E,Z*) analogue of the (*E,E*) darlingianine with structure (11) was confirmed by refluxing it with iodine in xylene: the isomerized product proved identical with darlingianine.

[9] Lukeš, R., Kovář, J., Kloubek, J., and Bláha, K., *Collect. Czech. Chem. Commun.*, 1960, **25**, 483.

Dihydrodarlingianine

This base had a molecular formula with two hydrogens more than darlingianine. The main absorption band in the u.v. spectrum was less intense and occurred at lower wavelength than that of darlingianine, and the spectrum was almost identical with that of 1-phenylprop-1-ene. Dihydrodarlingianine thus has one double bond only, between C 5 and C 6, and this deduction is consistent with the mass spectrometric and other spectroscopic data; the i.r. and n.m.r. spectra show the same general features as those of darlingianine, including evidence of a hydroxy group, an *N*-methylpyrrolidine nucleus, and an (*E*)-substituted double bond. The model compound 6-phenylhex-5-en-2-ol gave a similar u.v. spectrum, and showed similarities in those regions of the i.r. and ^{1}H n.m.r. spectra which corresponded to common structural features. The structure and stereochemistry of dihydrodarlingianine were confirmed by a controlled hydrogenation of darlingianine: the product on uptake of one molar proportion of hydrogen proved identical with dihydrodarlingianine, which is thus represented by (12).

Tetrahydrodarlingianine

The structure of this base was determined in a similar way from a comparison of its spectroscopic data with those of the above compounds, and of the model compound 6-phenylhexan-2-ol. Tetrahydrodarlingianine was prepared by catalytic hydrogenation of darlingianine; it thus has structure (13) and belongs to the same stereochemical series as the other bases.

C_{15} Pyrrolidine Bases

Dehydrodarlinine

This pale yellow alkaloid had u.v. and i.r. spectra consistent with a cinnamoyl chromophore with an (*E*) double bond: the model compound 4-phenylbut-3-en-2-one gave an identical u.v. spectrum. The mass spectrum of dehydrodarlinine showed a molecular ion at 26 mass units less than that of dehydrodarlingianine; this suggests that dehydrodarlinine is an analogue of the latter with one less conjugated olefinic group. The structure (14) was confirmed by a synthesis of the racemic base by condensing hygrine with benzaldehyde. The natural base has a positive rotation similar to that of dehydrodarlingianine, and a similar stereochemistry is assigned to it.

Darlinine and Epidarlinine

These isomeric bases gave evidence of a (*E*)-substituted styrene chromophore: the u.v. spectra were almost the same as that of the model compound 4-phenylbut-3-en-2-ol. Spectroscopic data also indicated the presence of a secondary alcohol group and an *N*-methylpyrrolidine nucleus in each case. The ^{1}H n.m.r. spectra of the two isomers were almost identical, and differed only in chemical shifts of protons H 2 and H 5′. The H 2 protons are attached to the chiral carbons which bear the hydroxy groups in each case, and the difference suggests that the bases have different configurations at this centre; on the other hand, the chemical shifts of the protons attached to C 2′, the other chiral centre, are the same for each isomer. The hydroxy groups are hydrogen-bonded to the nitrogens, and from Dreiding models one of the

protons attached to C 5′ would experience differential shielding effects if darlinine and epidarlinine were epimeric at C 2.

The structures of the two bases were confirmed by sodium borohydride reduction of dehydrodarlinine: a mixture of two diastereomeric alcohols was obtained, one of which proved identical with darlinine, the other with epidarlinine. In order to assign the correct configurations to these two alkaloids, a comparison was made of their ^{1}H n.m.r. spectra, specific rotations, and R_F values under the same conditions with those of darlingianine (10) and epidarlingianine, the artefact obtained along with the latter when dehydrodarlingianine (9) is reduced with borohydride. From the data in Table 1, darlinine is assigned the same configuration as darlingianine and is thus represented by (15), while the diastereomeric stereochemistry shown in (16) is attributed to epidarlinine.

Table 1. R_F values, ^{1}H n.m.r. data and specific rotations

Compound	R_F[A]	δ(H 5′)	δ(H 2)	$[\alpha]_D^{19}$ (degrees)
Darlinine	0·45	2·65	4·70	+75
Epidarlinine	0·30	2·83	4·48	+59
Darlingianine	0·40	2·63	4·60	+62
Epidarlingianine	0·25	2·72	4·38	+48

[A] For conditions, see Experimental.

Experimental

General

Microanalyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points were determined on a Yanagimoto Seisakusho micro-melting point apparatus and are uncorrected. Specific optical rotations were measured in chloroform solution on a Bellingham & Stanley polarimeter; u.v. absorption spectra were recorded with a Hitachi Perkin–Elmer 124 spectrophotometer; i.r. spectra were recorded on either a Beckman IR33 or a Perkin–Elmer 221 spectrophotometer; n.m.r. spectra were recorded in $CDCl_3$ solution on a Jeol JNM-4H 100-MHz or a Bruker HX-270 spectrometer with tetramethylsilane as internal standard; low-resolution mass spectra were run on an EAI Quad 300 spectrometer, employing an inlet temperature of 250° and an electron beam energy maintained at 70 eV; high-resolution mass spectra were run on an A.E.I. MS 902 spectrometer operating at 70 eV with a source temperature of 150°, the direct insertion technique being used. Analytical and preparative t.l.c. were carried out on Camag DSF-5 silica gel, either basic, prepared by pretreatment with 0·5 N KOH (basic silica gel), or neutral.

Alkaloid Extraction

Air-dried and finely ground upper stems and leaves (9 kg) of *Darlingia darlingiana* collected from Davies Creek, north Queensland, were exhaustively extracted with methanol at room temperature. The extract was concentrated in vacuum at a temperature below 35° to a syrupy liquid (1·5 l.), which was dissolved in warm glacial acetic acid (1·5 l.). The liquid was poured in a fine stream into 15 l. of water whilst the solution was rapidly agitated with a vibromixer. The solution was left to stand overnight, and a precipitate that settled out was filtered off, washed with water until free from alkaloids, then discarded. The washings, combined with the acid aqueous solution, were basified to pH 8 with ammonia (d 0·880) and extracted with chloroform (8 × 1 l.). The emulsion formed each time was broken either by centrifugation or by filtration through Hi-Flo Supercel; the resultant precipitate, which still gave a positive Mayer test, was extracted with warm chloroform, or alternatively redissolved in warm glacial acetic acid and then reworked by repeating the above procedure. The total chloroform extract was washed once with water, dried (Na_2SO_4), concentrated to half volume, and then extracted with 5% v/v sulfuric acid until the acid extracts were Mayer negative (10 × 300 ml). The acid solution was then basified with ammonia and extracted with chloroform

(16 × 300 ml). The chloroform solution was washed once with water, dried (Na_2SO_4), and evaporated to dryness in vacuum to give a viscous strong smelling brown oil (20 g, 0·22% yield).

Separation of Bases

The crude alkaloid mixture (20 g) was dissolved in chloroform and subjected to Craig countercurrent distribution with chloroform as the stationary phase and $0{\cdot}5 \times 10^{-3}$ M sulfuric acid as the mobile phase (*c.* 40 ml per transfer). Every tenth fraction was monitored by t.l.c. after concentration, basification and extraction of the aqueous eluent with chloroform. The fractions were bulked accordingly and the bulking summary is tabulated below, the total weight of alkaloid recovered being 16·11 g:

Tube	1–71	72–300	301–905	906–1027	1028–1198	1199–1215	1216–1432
Fraction	1	2	3	4	5	6	7
Alkaloid recovered (g)	0·39	2·01	8·98	1·75	1·90	0·14	0·94

Isolation, Purification and Characterization of the Alkaloids

Fraction 1

Analytical t.l.c. (12% MeOH/$CHCl_3$) revealed the presence of one major and three minor components. P.t.l.c. on a 1-m plate (basic silica gel; 10% Et_3N/$CHCl_3$) enabled the separation of the major component, 2-acetyltrop-2-ene (ferruginine) (36 mg). Its identity was established by a direct comparison of its R_F, $[\alpha]_D$, u.v., i.r., ^1H n.m.r. and m.s. data with those of the authentic base isolated from *D. ferruginea*.[6] Ferruginine formed a picrate, m.p. 161–163°.

The minor components were isolated in amounts too small for further studies.

Fraction 2

This semicrystalline fraction on dilution with ether/light petroleum and chilling overnight deposited white crystalline material (890 mg), which was twice recrystallized from ether to give white needles of darlingine, m.p. 166–167°, $[\alpha]_D^{19}$ +104° ($CHCl_3$); R_F 0·75 (12% MeOH/$CHCl_3$), 0·65 (10% Et_3N/$CHCl_3$) (Found: C, 70·9; H, 7·7; N, 6·2. Calc. for $C_{13}H_{17}NO_2$: C, 71·2; H, 7·7; N, 6·4%). λ_{max} (EtOH): 258 (logε 4·03), 217 nm (4·01). ν_{max} (Nujol): 1660 (α,β-unsaturated carbonyl), 1610 (olefinic), 1145, 1175 cm^{-1} (symmetrical and asymmetrical ν_{C-O} stretch). ^1H n.m.r. δ: 4·19, d, $J_{6,7}$ 4·3 Hz, 1H, H6; 3·48, t, $J_{9,8}$ 5·1, $J_{9,10eq}$ 5 Hz, 1H, H9; 3·02, dd, $J_{10eq,9}$ 5·1, $J_{10eq,10ax}$ 17·5 Hz, 1H, H10*eq*; 2·35, s, 3H, NCH_3; 2·25, s, 3H, CCH_3; 2·12, d, $J_{10ax,10eq}$ 17·5 Hz, 1H, H10*ax*; 1·92, s, 3H, CCH_3. ^{13}C n.m.r. δ: 177·7, s, C4; 161·1, s, C11; 159·9, s, C2; 123·9, s, C5; 120·7, s, C3; 58·4, d, C6; 56·1, d, C9; 37·3, q, NCH_3; 34·0, t, C7 and C8; 29·8, t, C10; 18·3, q, 2-CH_3; 10·4, q, 3-CH_3. Mass spectrum: *m/z* 219 (64%, M) (Found: 219·1268; calc. for $C_{13}H_{17}NO_2$: 219·1270), 191 (45), 190 (100), 163 (15), 136 (21), 110 (2), 109 (5), 96 (35), 95 (26), 92 (13), 82 (36), 81 (30), 42 (27). The identity of this major alkaloid was established by a direct comparison of its m.p., m.m.p., R_F, u.v., i.r., n.m.r. and m.s. data with those of authentic darlingine isolated previously.[4] Darlingine forms a hydrochloride, fine white needles, m.p. 180–182°. ^1H n.m.r. δ: 6·42, br, 1H, ^+NH; 4·82, d, $J_{6,7}$ 4·3 Hz, 1H, H6; 4·33, br m, 1H, H9; 3·67, m, 1H, H10*eq*; 2·92, s, 3H, NCH_3; 2·70, d, $J_{10ax,10eq}$ 17·5 Hz, 1H, H10*ax*; 2·32, s, 3H, CCH_3; 1·94, s, 3H, CCH_3.

The mother liquor after removal of darlingine was subjected to p.t.l.c. (12% MeOH/$CHCl_3$). The major, higher R_F band was found to be darlingine, which crystallized easily as white needles after p.t.l.c. purification. A new alkaloid (89 mg), named darlinine, was isolated from the lower R_F band, with R_F 0·45 (MeOH/$CHCl_3$/NH_3 15 : 85 : 1) and 0·68 (10% Et_3N/$CHCl_3$). *Darlinine* was recrystallized from ethanol to give straw-coloured crystals, m.p. 59–61°, $[\alpha]_D^{19}$ +75° ($CHCl_3$) (Found: C, 77·6; H, 9·0; N, 5·9. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·1; N, 6·1%). λ_{max} (EtOH): 211 (logε 4·27), 251 nm (4·22). ν_{max} ($CHCl_3$): 3250 (hydroxy), 1595 (olefinic), 960 [(*E*)-disubstituted double bond], 742, 685 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·30, m, 5H, ArH; 6·63, d, $J_{4,3}$ 16 Hz, 1H, H4; 6·20, dd, $J_{3,2}$ 6, $J_{3,4}$ 16 Hz, 1H, H3; 4·88, br, variable depending on concn, exchangeable with D_2O, 1H, OH; 4·70, br m, 1H, allylic H2; 3·10, br m, 1H, NCH; 2·65, br m, 1H, NCH; 2·38, s, 3H, NCH_3; 2·35–1·30, m, 7H, aliphatic. Mass spectrum: *m/z* 231 (5%, M) (Found: 231·1621; $C_{15}H_{21}NO$ requires 231·1619), 126 (7, $C_7H_{12}NO$), 97 (5, $C_6H_{11}N$), 96 (3), 91 (2), 84 (100, $C_5H_{10}N$), 42 (8, C_2H_4N).

Fraction 3

This semicrystalline fraction also deposited crystals of darlingine upon careful dilution with ether/light petroleum and chilling overnight. After removal of the crystalline material (2·65 g), the mother liquor was subjected to p.t.l.c. ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1). The highest R_F band again proved to be darlingine. The intermediate band gave a new base (62 mg), epidarlinine, a diastereoisomer of darlinine. On repeated crystallization from ethanol, *epidarlinine* gave straw-coloured crystals, m.p. 66–68°, $[\alpha]_D^{19}$ +59° ($CHCl_3$); R_F 0·30 ($MeOH/CHCl_3/NH_3$ 15 : 85 : 1) and 0·47 (10% $Et_3N/CHCl_3$) (Found: C, 77·7; H, 9·0; N, 5·9. $C_{15}H_{21}NO$ requires C, 77·9; H, 9·1; N, 6·1%). λ_{max} (EtOH): 211 ($\log\varepsilon$ 4·27), 251 nm (4·22). ν_{max} ($CHCl_3$): 3260 (hydroxy), 1600 (olefinic), 962 [(*E*)-disubstituted double bond], 743, 688 cm^{-1} (monosubstituted benzene). ^1H n.m.r. δ: 7·35, m, 5H, ArH; 6·65, d, $J_{4,3}$ 16 Hz, 1H, H4; 6·25, dd, $J_{3,2}$ 6, $J_{3,4}$ 16 Hz, 1H, H3; 4·59, br, variable depending on concn, exchangeable with D_2O, 1H, OH; 4·48, br m, 1H, allylic H2; 3·12, br m, 1H, NCH; 2·83, br m, 1H, NCH; 2·42, s, 3H, NCH_3; 2·4–1·4, m, 7H, aliphatic. Mass spectrum: *m/z* 231 (6%, M, $C_{15}H_{21}NO$), 126 (10), 97 (9), 96 (4), 91 (1), 84 (100), 42 (12).

The band of lowest R_F initially gave an oil. Analytical t.l.c. with several different solvent systems revealed that it was a mixture of three components, of almost identical or very close R_F values. None of these solvent systems alone, however, produced a total separation, and the most effective procedure was as follows: P.t.l.c. was carried out on basic silica gel, in three successive multiple developments with 5, 7 and 9% $MeOH/CHCl_3$. Three bands became distinctly discernible, each of which was extracted, and the recovered bases were again purified by p.t.l.c., the same development procedure being used. The highest R_F component (160 mg) was found to be a new base, *dihydrodarlingianine*; initially a clear oil, it finally crystallized from ethanol as light straw-coloured crystals, m.p. 72–74°, $[\alpha]_D^{19}$ +34° ($CHCl_3$); R_F 0·81 (10% $Et_3N/CHCl_3$), 0·56 ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1) and 0·31 ($MeOH/NH_3$ 100 : 1·5) (Found: C, 78·5; H, 9·8; N, 5·1. $C_{17}H_{25}NO$ requires C, 78·8; H, 9·7; N, 5·4%). λ_{max} (EtOH): 211 ($\log\varepsilon$ 4·25), 251 nm (4·21). ν_{max} ($CHCl_3$): 3260 (hydroxy), 1600 (olefinic), 965 [(*E*)-disubstituted double bond], 740, 688 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·28, m, 6H, 5ArH+H6; 6·36, m, 1H, H5; 5·63, br, exchangeable with D_2O, 1H, OH; 4·03, br m, 1H, H2; 3·08, br m, 1H, NCH; 2·60, br m, 1H, NCH; 2·36, s, 3H, NCH_3; 2·5–1·1, m, 11H, aliphatic. Mass spectrum: *m/z* 259 (19%, M) (Found: 259·1943; $C_{17}H_{25}NO$ requires 259·1936), 126 (11), 97 (4), 96 (2), 91 (6), 84 (100, $C_5H_{10}N$), 42 (8).

The intermediate R_F component (43 mg) proved to be a new base, *isodarlingianine*, which had R_F 0·78 (10% $Et_3N/CHCl_3$), 0·52 ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1) and 0·30 ($MeOH/NH_3$ 100 : 1·5). Initially a clear oil, it finally crystallized from light petroleum as straw-coloured crystals, m.p. 50–52°, $[\alpha]_D^{19}$ +47° ($CHCl_3$) (Found: C, 79·6; H, 8·7; N, 5·4. $C_{17}H_{23}NO$ requires C, 79·4; H, 9·0; N, 5·5%). λ_{max} (EtOH): 214 ($\log\varepsilon$ 4·16), 274 nm (4·24). ν_{max} ($CHCl_3$): 3210 (hydroxy), 1598, 985, 942, 908 (olefinic, disubstituted double bonds), 768, 695 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·28, m, 5H, ArH; 6·80, dd, $J_{4,3}$ 16, $J_{4,5}$ 9 Hz, 1H, H4; 6·30, m, 2H, H5 and H6; 5·85, dd, $J_{3,2}$ 6, $J_{3,4}$ 16 Hz, 1H, H3; 5·20, br, exchangeable with D_2O, 1H, OH; 4·58, br m, 1H, allylic H2; 3·11, br m, 1H, NCH; 2·65, br m, 1H, NCH; 2·38, s, 3H, NCH_3; 2·35–1·48, m, 7H, aliphatic. Mass spectrum: *m/z* 257 (8%, M) (Found: 257·1776; $C_{17}H_{23}NO$ requires 257·1779), 156 (3), 126 (9), 97 (5), 96 (2), 91 (4), 84 (100, $C_5H_{10}N$), 42 (25).

The lowest R_F component (262 mg), the major constituent of the initial mixture of three, proved to be another new base, *darlingianine*. On recrystallization from ethanol, it afforded straw-coloured rhombic crystals, m.p. 93·5°, $[\alpha]_D^{19}$ +62° ($CHCl_3$); R_F 0·75 (10% $Et_3N/CHCl_3$), 0·35 ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1) and 0·28 ($MeOH/NH_3$ 100 : 1·5) (Found: C, 79·5; H, 8·9; N, 5·3. $C_{17}H_{23}NO$ requires C, 79·4; H, 9·0; N, 5·5%). λ_{max} (EtOH): 207 ($\log\varepsilon$ 4·26), 285 nm (4·36). ν_{max} (Nujol): 3180 (hydroxy), 1585 (olefinic), 990 [(*E*)-disubstituted double bond], 740, 685 cm^{-1} (monosubstituted benzene ring). ν_{max} ($CHCl_3$): 3190 cm^{-1} (no change on dilution—intramolecularly bonded hydroxyl). ^1H n.m.r. δ: 7·29, m, 5H, ArH; 6·80, dd, $J_{4,3}$ 16, $J_{4,5}$ 9 Hz, 1H, H4; 6·50, d, $J_{6,5}$ 16 Hz, 1H, H6; 6·45, dd, $J_{5,6}$ 16, $J_{5,4}$ 9 Hz, 1H, H5; 5·82, dd, $J_{3,4}$ 16, $J_{3,2}$ 6 Hz, 1H, H3; 4·60, br m, 1H, allylic H2; 3·08, br m, 1H, NCH; 2·63, br m, 1H, NCH; 2·35, s, 3H, NCH_3. ^{13}C n.m.r. δ: 56·4, t, C5′; 23·1, t, C4′; 28·0, t, C3′; 64·2, d, C2′; 35·4, t, C1; 68·6, d, C2; 130·5, d, C3; 128·0, d, C5 or C4; 127·5, d, C4 or C5; 135·8, d, C6; 136·0, s, C1″; 125·0, d, C2″ and C6″; 127·2, d, C3″ and C5″; 126·0, d, C4″; 40·3, q, NCH_3. Mass spectrum: *m/z* 257 (25%, M) (Found: 257·1778; $C_{17}H_{23}NO$ requires 257·1779), 156 (3, $C_{12}H_{12}$), 130 (1, $C_{10}H_{10}$), 126 (24, $C_7H_{12}NO$), 97 (4, $C_6H_{11}N$), 96 (2), 91 (4, C_7H_7), 84 (100, $C_5H_{10}N$), 42 (13, C_2H_4N).

Fraction 4

When subjected to p.t.l.c. ($MeOH/CHCl_3/NH_3$ 11 : 89 : 1), this fraction separated into three bands. After further p.t.l.c. purification, an oil (42 mg) was isolated from the highest R_F band, which appeared homogeneous on t.l.c., R_F 0·81 ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1), 0·59 ($MeOH/NH_3$ 100 : 1·5) and 0·88 (10% $Et_3N/CHCl_3$), but could not be induced to crystallize. It proved to be a new alkaloid, *5,11-dihydrodarlingine*, $[\alpha]_D^{19}$ +37° ($CHCl_3$). λ_{max} (EtOH): 271 nm ($\log\varepsilon$ 3·83). ν_{max} ($CHCl_3$): 1658 (α,β-unsaturated carbonyl), 1608 cm^{-1} (olefinic). ^1H n.m.r. δ: 4·13, m, 1H, H11; 3·99, m, 1H, H6; 3·70, m, 1H, H9; 3·28, m, 1H, H5; 2·33, s, 3H, NCH_3; 1·99, s, 3H, CCH_3; 1·70, s, 3H, CCH_3. Mass spectrum: *m/z* 221 (11%, M) (Found: 221·1418; $C_{13}H_{19}NO_2$ requires 221·1416), 193 (7), 192 (31), 178 (2), 150 (2), 122 (8), 97 (34), 96 (18), 95 (19), 94 (39), 82 (100), 81 (96), 57 (31), 42 (47). The base formed a *picrate*, m.p. 165–168°.

The second band contained darlingine, and the third was found to consist of a mixture of the three alkaloids isolated earlier: darlingianine, dihydrodarlingianine and isodarlingianine. These three bases were separated by the procedure previously described.

Fraction 5

This fraction gave two distinct bands on p.t.l.c. ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1). From the upper band, easily located by its dark purplish fluorescence under 350-nm u.v. light, a new alkaloid, *dehydrodarlinine*, was isolated; after further p.t.l.c. purification it was obtained as a clear oil (32 mg) which crystallized from light petroleum as pale yellow plates, m.p. 42–44°, $[\alpha]_D^{19}$ +64° ($CHCl_3$); R_F 0·55 ($MeOH/CHCl_3/NH_3$ 15 : 85 : 1) and 0·46 ($MeOH/NH_3$ 100 : 1·5) (Found: C, 78·8; H, 8·2; N, 5·9. $C_{15}H_{19}NO$ requires C, 78·6; H, 8·3; N, 6·1%). λ_{max} (EtOH): 220 ($\log\varepsilon$ 4·04), 288 nm (4·34). ν_{max} ($CHCl_3$): 1688, 1660 (α,β-unsaturated carbonyl), 1605 (olefinic), 975 [(*E*)-disubstituted double bond], 745, 685 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·45, m, 6H, 5ArH+H4; 6·75, d, $J_{3,4}$ 16 Hz, 1H, H3; 2·36, s, 3H, NCH_3. Mass spectrum: *m/z* 229 (4%, $C_{15}H_{19}NO$, M), 131 (7, C_9H_7O), 97 (20), 96 (2), 84 (100, $C_5H_{10}N$), 42 (36).

The lower band proved to be a mixture of darlingianine, dihydrodarlingianine and isodarlingianine. The three bases were separated by the procedure described earlier.

Fraction 6

Application of p.t.l.c. ($MeOH/CHCl_3/NH_3$ 11 : 89 : 1) to this fraction yielded two bands; the upper one, easily distinguished by its dark purplish fluorescence under 350-nm u.v. light, gave partly crystalline material (55 mg) which on recrystallization from light petroleum afforded pale yellow *plates*, m.p. 54–55°, $[\alpha]_D^{19}$ +53° ($CHCl_3$) (Found: C, 80·0; H, 8·2; N, 5·4. $C_{17}H_{21}NO$ requires C, 80·0; H, 8·2; N, 5·5%). This new alkaloid, dehydrodarlingianine, had R_F 0·62 (basic silica gel; 8% $MeOH/CHCl_3$); R_F 0·88 (10% $Et_3N/CHCl_3$). λ_{max} (EtOH): 233 ($\log\varepsilon$ 3·78), 322 nm (4·51). ν_{max} (Nujol): 1675 (α,β-unsaturated carbonyl), 1605, 1585 (olefinic), 998 [(*E*)-disubstituted double bond], 740, 680 cm^{-1} (monosubstitution in a benzene ring). ^1H n.m.r. δ: 7·36, m, 6H, 5ArH+H6; 6·90, m, 2H, H5 and H4; 6·30, d, $J_{3,4}$ 16 Hz, 1H, H3; 2·35, s, 3H, NCH_3. Mass spectrum: *m/z* 255 (13%, M) (Found: 255·1599; $C_{17}H_{21}NO$ requires 255·1596), 157 (4, $C_{11}H_9O$), 97 (63, $C_6H_{11}N$), 96 (2), 91 (1), 84 (100, $C_5H_{10}N$), 42 (22, C_2H_4N).

The lower band (faint u.v. absorbing) gave a clear oil (34 mg) which after further p.t.l.c. purification appeared homogeneous, with R_F 0·83 (10% $Et_3N/CHCl_3$), 0·58 ($MeOH/CHCl_3/NH_3$ 12 : 88 : 1) and 0·28 ($MeOH/NH_3$ 100 : 1·5). This new base, *tetrahydrodarlingianine*, which could not be induced to crystallize, had $[\alpha]_D^{19}$ +22° ($CHCl_3$). λ_{max} (EtOH): 212 nm ($\log\varepsilon$ 3·78). ν_{max} (film): 3270 (hydroxy), 745, 698 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·23, m, 5H, ArH; 5·22, br, exchangeable with D_2O, 1H, OH; 3·97, br m, 1H, H2; 3·55, br m, 1H, NCH; 3·13, br m, 1H, NCH; 2·64, m, 2H, benzylic; 2·37, s, 3H, NCH_3; 2·35–1·10, m, 13H, aliphatic. Mass spectrum: *m/z* 261 (2%, M) (Found: 261·1998; $C_{17}H_{27}NO$ requires 261·1995), 170 (1), 126 (7), 97 (7), 96 (3), 91 (15, C_7H_7), 84 (100, $C_5H_{10}N$), 42 (28). Tetrahydrodarlingianine formed a *picrate*, m.p. 178–181°.

Fraction 7

Analytical t.l.c. revealed a single component in this semicrystalline fraction. On careful dilution with light petroleum and chilling overnight, it deposited crystalline material (161 mg), which was twice recrystallized from light petroleum to give pale yellow plates, m.p. 54–55°, $[\alpha]_D^{19}$ +53° ($CHCl_3$).

T.l.c. (distinct dark purplish fluorescence under 350-nm u.v. light), and spectroscopic characteristics (u.v., i.r., ^{1}H n.m.r. and m.s.), established that this alkaloid was dehydrodarlingianine, isolated in fraction 6. The mother liquor was concentrated, diluted with light petroleum, then chilled overnight again, whereupon another crop of dehydrodarlingianine was obtained.

O-Acetylation of Darlingianine

Darlingianine (60 mg) was treated with acetic anhydride (1 ml) in anhydrous pyridine (4 ml). The solution was stirred at room temperature for 12 h, water was added, then the solution was extracted with chloroform. The chloroform extract was washed three times with water, dried (Na_2SO_4), and evaporated to dryness in vacuum. The residue (58 mg) was recrystallized from ethanol to give *O*-acetyldarlingianine, m.p. 82–85°, R_F 0·51 (MeOH/$CHCl_3$/NH_3 10 : 90 : 1). λ_{max} (EtOH): 285 nm (log ε 4·36). ν_{max} ($CHCl_3$): 1738 (carbonyl of acetate), 985 [(*E*)-disubstituted double bond], 745, 688 cm^{-1} (monosubstituted benzene ring). ^{1}H n.m.r. δ: 7·32, m, 5H, ArH; 6·78, dd, $J_{4,3}$ 16, $J_{4,5}$ 9 Hz, 1H, H4; 6·49, d, $J_{6,5}$ 16 Hz, 1H, H6; 6·43, dd, $J_{5,6}$ 16, $J_{5,4}$ 9 Hz, 1H, H5; 5·80, dd, $J_{3,4}$ 16, $J_{3,2}$ 6 Hz, 1H, H3; 5·42, br m, 1H, allylic H2; 3·35, br m, 1H, NCH; 3·09, br m, 1H, NCH; 2·32, s, 3H, NCH_3; 2·08, s, 3H, $COCH_3$; 2·3–1·1, m, 7H, aliphatic. Mass spectrum: *m/z* 299 (M).

N-Methiodide of Darlingianine

Darlingianine (50 mg) in warm methanol (5 ml) was treated with methyl iodide (0·2 ml). The solution was gently refluxed for 2 h, cooled, then evaporated to dryness. The residue (65 mg) was recrystallized from methanol to give *darlingianine methiodide*, m.p. 123–126° (Found: C, 53·8; H, 6·7; N, 3·4. $C_{18}H_{26}INO$ requires C, 54·1; H, 6·5; N, 3·5%).

Preparation of Model Compounds

6-Phenylhexa-3,5-dien-2-one

Prepared according to the procedure of Diehl and Einhorn,[10] 6-phenylhexa-3,5-dien-2-one formed large pale yellow rhombic plates, m.p. 67–68° (lit.[10] 68°), after recrystallization from ether. It gave a distinct purple fluorescence under 350-nm u.v. light, and had R_F 0·70 (4% MeOH/$CHCl_3$). λ_{max} (EtOH): 319 (log ε 4·52), 233 nm (3·77). ν_{max} (Nujol): 1665, 1648 (α,β-unsaturated carbonyl), 1612 (olefinic), 978 [(*E*)-disubstituted double bond], 739, 681 cm^{-1} (monosubstituted benzene ring). ^{1}H n.m.r. δ: 7·33, m, 6H, 5ArH+H6; 6·91, m, 2H, H4 and H5; 6·22, d, $J_{3,4}$ 16 Hz, 1H, H3; 2·27, s, 3H, CH_3. Mass spectrum: *m/z* 172 (M).

6-Phenylhexa-3,5-dien-2-ol

A solution of 6-phenylhexa-3,5-dien-2-one (293 mg) in aqueous methanol (20 ml, 95%) was slowly treated with $NaBH_4$ (145 mg); after the spontaneous reaction had subsided, the pale yellow solution turned colourless. The solution was gently refluxed for 15 min, cooled, diluted with water, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness in vacuum to give a white crystalline residue (281 mg). T.l.c. (4% MeOH/$CHCl_3$) showed a single spot with R_F 0·62. The residue was recrystallized from ether to give colourless crystals, m.p. 69–70° (lit.[11] 65–66°). λ_{max} (EtOH): 285 nm (log ε 4·36). ν_{max} (Nujol): 3280 (hydroxy), 985 [(*E*)-disubstituted double bond], 740, 685 cm^{-1} (monosubstituted benzene ring). ^{1}H n.m.r. δ: 7·28, m, 5H, ArH; 6·75, dd, $J_{4,3}$ 16, $J_{4,5}$ 9 Hz, 1H, H4; 6·47, d, $J_{6,5}$ 16 Hz, 1H, H6; 6·33, dd, $J_{5,4}$ 9, $J_{5,6}$ 16 Hz, 1H, H5; 5·81, dd, $J_{3,2}$ 6, $J_{3,4}$ 16 Hz, 1H, H3; 4·37, br m, 1H, allylic, H2; 2·25, app. d (br), exchangeable with D_2O, 1H, OH; 1·30, d, *J* 6 Hz, 3H, CH_3. Mass spectrum: *m/z* 174 (M).

4-Phenylbut-3-en-2-one

This ketone was prepared according to the procedure of Drake and Allen.[12] The yellow oil crystallized on chilling, and after recrystallization from light petroleum formed yellow crystals, m.p.

[10] Diehl, L., and Einhorn, A., *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 2320.
[11] Macbeth, A. K., and Mills, J. A., *J. Chem. Soc.*, 1949, 2646.
[12] Drake, N. L., and Allen, P., *Org. Synth.*, 1923, **3**, 17.

41–42° (lit.[12] 40–42°). It gave a distinct purple fluorescence under 350-nm u.v. light and had R_F 0·80 (3% MeOH/$CHCl_3$). λ_{max} (EtOH): 286 ($\log\varepsilon$ 4·35), 220 nm (4·09). ν_{max} (Nujol): 1691, 1675 (α,β-unsaturated carbonyl), 1610 (olefinic), 970 [(*E*)-disubstituted double bond], 745, 688 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·42, m, 6H, ArH+H4; 6·68, d, $J_{3,4}$ 16 Hz, 1H, H3; 2·34, s, 3H, CH_3. Mass spectrum: *m/z* 146 (M).

4-Phenylbut-3-en-2-ol

A solution of 4-phenylbut-3-en-2-one (358 mg) in aqueous methanol (15 ml, 95%) was slowly treated with $NaBH_4$ (160 mg), and, after the spontaneous reaction had subsided, the pale yellow solution turned colourless. The solution was gently refluxed for 15 min, cooled, diluted with water and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness in vacuum to give a clear colourless oil (343 mg). T.l.c. (3% MeOH/$CHCl_3$) showed a single spot with R_F 0·70. The oil, on chilling and recrystallization from light petroleum, formed colourless crystals, m.p. 42–44° (lit.[13] 39–41°). λ_{max} (EtOH): 251 nm ($\log\varepsilon$ 4·23). ν_{max} ($CHCl_3$): 3340 (hydroxy), 1595 (olefinic), 960 [(*E*)-disubstituted double bond], 742, 687 cm^{-1} (monosubstituted benzene ring). ^1H n.m.r. δ: 7·32, m, 5H, ArH; 6·54, d, $J_{4,3}$ 16 Hz, 1H, H4; 6·21, dd, $J_{3,2}$ 6, $J_{3,4}$ 16 Hz, 1H, H3; 4·45, br m, 1H, allylic H2; 2·55, app. d (br), exchangeable with D_2O, 1H, OH; 1·34, d, *J* 6 Hz, 3H, CH_3. Mass spectrum: *m/z* 148 (M).

6-Phenylhex-5-en-2-ol

A solution of 6-phenylhexa-3,5-dien-2-ol (35 mg) in ethanol (3 ml) was carefully hydrogenated in the presence of 10% Pd/C (3 mg) at room temperature and atmospheric pressure. The course of the hydrogenation was monitored by u.v. spectroscopy: the 285-nm peak of the hexadienol slowly shifted to 251 nm, the peak of the required hexenol, thus marking the end of the hydrogenation (20–40 min). If hydrogen uptake is too rapid, the second double bond is also reduced, the formation of the tetrahydro product being evidenced by the appearance of a 212-nm peak. Under the correct conditions for formation of the dihydro product, hydrogen uptake corresponded closely to 1 mol. equiv. per mole of the alcohol. In some experiments a mixture of dihydro and tetrahydro products was obtained, which could be separated by p.t.l.c. (4% MeOH/$CHCl_3$). The dihydro product furnished a clear oil which was purified by p.t.l.c.; it was homogeneous on t.l.c., R_F 0·68 (4% MeOH/$CHCl_3$). λ_{max} (EtOH): 251 nm ($\log\varepsilon$ 4·22). ν_{max} (film): 3350 (hydroxy), 1600 (olefinic), 965 [(*E*)-disubstituted double bond], 740, 687 cm^{-1} (monosubstituted benzene). ^1H n.m.r. δ: 7·27, m, 6H, 5ArH+H6; 6·33, m, 1H, H5; 3·80, br m, 1H, H2; 2·21, br, variable depending on concn, exchangeable with D_2O, 1H, OH; 1·20, d, *J* 6 Hz, 3H, CH_3. Mass spectrum: *m/z* 176 (M).

6-Phenylhexan-2-ol

A solution of 6-phenylhexa-3,5-dien-2-ol (40 mg) in ethanol (3 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% Pd/C (3 mg). When the compound had taken up hydrogen corresponding to 2 mol. equiv. per mole of alcohol, further uptake stopped. The filtered solution upon evaporation furnished a clear oil which could not be induced to crystallize. The product was homogeneous on t.l.c., R_F 0·72 (4% MeOH/$CHCl_3$). λ_{max} (EtOH): 212 nm ($\log\varepsilon$ 3·78). ν_{max} (film): 3360 (hydroxy), 745, 698 cm^{-1} (monosubstituted benzene). ^1H n.m.r. δ: 7·18, m, 5H, ArH; 3·75, br m, 1H, H2; 2·62, app. t, 2H, benzylic; 2·18, br, variable depending on concn, exchangeable with D_2O, 1H, OH; 1·9–1·3, br m, 6H, $3CH_2$; 1·16, d, *J* 6 Hz, 3H, CH_3. Mass spectrum: *m/z* 178 (M).

Hydrogenation of 6-Phenylhexa-3,5-dien-2-one

Hydrogenation of the phenylhexadienone (λ_{max} 319 nm) at room temperature and atmospheric pressure in the presence of 10% Pd/C resulted initially in the formation of the corresponding dienol (λ_{max} 285 nm). Further hydrogenation produced the hexenol (λ_{max} 251 nm), and finally the hexanol (λ_{max} 212 nm). The phenyl ring was not hydrogenated under the conditions used.

[13] Červinka, O., and Kříž, O., *Collect. Czech. Chem. Commun.*, 1973, **38**, 294.

Synthesis of Hygrine

Hygrine was synthesized either from *N*-methylpyrrolidin-2-one and acetoacetic acid by the method of Galinovsky *et al.*,[14,15] or from *N*-methylpyrrolidine and ethyl acetoacetate by the method of Leonard and Cook.[16] It was obtained as a mobile oil, b.p. 76–77°/11 mm (lit.[16] 83°/19 mm). ν_{max} (film): 1708s cm^{-1} (aliphatic ketone). ^1H n.m.r. δ: 3·2–1·2, m, 9H, aliphatic; 2·30, s, 3H, NCH_3; 2·18, s, 3H, $COCH_3$. Mass spectrum: *m/z* 141 (8%, M), 126 (1), 98 (6), 70 (4), 84 (100), 42 (25). Hygrine formed a picrate which after recrystallization from ethanol had m.p. 149–151° (lit.[16] 149·5–151°).

Synthesis of Dehydrodarlingianine

A cooled solution of hygrine (230 mg) in ethanol (7 ml) was treated with freshly distilled cinnamaldehyde (420 mg), then 10% NaOH (3 ml) was added dropwise to the slowly stirred solution. The mixture was left in the dark at *c.* 5° for 2 h; ethanol was removed in vacuum and the thick solution was diluted with water (7 ml) and extracted with chloroform (5 × 5 ml). The chloroform extract was washed with water and extracted with 5% sulfuric acid (6 × 6 ml); the aqueous acid solution was basified with ammonia (*d* 0·880) and extracted with chloroform (5 × 7 ml). The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated in vacuum to an oil, which was purified by p.t.l.c. ($MeOH/CHCl_3/NH_3$ 10 : 90 : 1). A clear oil (149 mg, 36% yield) was obtained, which crystallized from light petroleum as pale yellow plates, m.p. 42–43° (Found: C, 80·3; H, 8·2; N, 5·4. Calc. for $C_{17}H_{21}NO$: C, 80·0; H, 8·2; N, 5·5%). The product proved identical in R_F, u.v., i.r., n.m.r. and m.s. data with natural dehydrodarlingianine; it was, however, optically inactive.

Reduction of Dehydrodarlingianine

Synthetic dehydrodarlingianine (120 mg) in aqueous methanol (20 ml, 95%) was slowly treated with $NaBH_4$ (60 mg), and after the spontaneous reaction had subsided the solution was gently refluxed for 20 min, cooled, diluted with water (40 ml), and extracted with chloroform (4 × 20 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness in vacuum. T.l.c. on the white residue ($MeOH/CHCl_3/NH_3$ 15 : 85 : 1) revealed two spots (R_F 0·40 and 0·25) of about equal intensity, neither of which corresponded to the starting ketone. The residue was subjected to p.t.l.c., whereupon two products were isolated.

Product 1 (54 mg), R_F 0·40, initially a clear oil, crystallized slowly on standing, and upon recrystallization from ethanol formed straw-coloured rhombs, m.p. 82–83°. It proved identical in R_F, u.v., i.r., n.m.r. and m.s. data with the natural base darlingianine; it was, however, optically inactive.

Product 2 (54 mg), R_F 0·25, crystallized more readily than product 1, and on recrystallization from ethanol gave almost colourless glassy rhombs, m.p. 90–91°, of epidarlingianine. Its u.v., i.r. and m.s. data were all similar to darlingianine. ^1H n.m.r. δ: 7·28, m, 5H, ArH; 6·79, dd, $J_{4,3}$ 16, $J_{4,5}$ 9 Hz, 1H, H4; 6·49, d, $J_{6,5}$ 16 Hz, 1H, H6; 6·44, dd, $J_{5,6}$ 16, $J_{5,4}$ 9 Hz, 1H, H5; 5·82, dd, $J_{3,4}$ 16, $J_{3,2}$ 6 Hz, 1H, H3; 4·62, br, exchangeable with D_2O, 1H, OH; 4·38, br m, 1H, allylic H2; 3·05, br m, 1H, NCH; 2·72, br m, 1H, NCH; 2·37, s, 3H, NCH_3; 2·35–1·30, m, 7H, aliphatic.

Natural dehydrodarlingianine on reduction with $NaBH_4$ by the same procedure also gave two products in about equal proportions. The first product was identical with natural darlingianine in all respects (including optical rotation) and corresponded to product 1 from the reduction of synthetic dehydrodarlingianine in R_F, u.v., i.r., ^1H n.m.r. and m.s. data. The second product corresponded to product 2 from reduction of synthetic dehydrodarlingianine (epidarlingianine) in R_F, u.v., i.r., n.m.r. and m.s. data; it was, however, optically active with $[\alpha]_D^{19}$ +48° ($CHCl_3$), m.p. 96–98°.

Synthesis of Dehydrodarlinine

A cooled solution of hygrine (229 mg) in ethanol (7 ml) was treated with freshly distilled benzaldehyde (340 mg), then 10% NaOH (3 ml) was added dropwise to the slowly stirred solution. The

[14] Galinovsky, F., Wagner, A., and Weiser, R., *Monatsh. Chem.*, 1951, **82**, 551.
[15] Galinovsky, F., and Zuber, H., *Monatsh. Chem.*, 1953, **84**, 798.
[16] Leonard, N. J., and Cook, A. G., *J. Am. Chem. Soc.*, 1959, **81**, 5627.

mixture was left in the dark at *c.* 5° for 2 h, then ethanol was evaporated off in vacuum; water (7 ml) was added and the aqueous solution was extracted with chloroform (5 × 5 ml). The chloroform solution was washed with water and extracted with 5% sulfuric acid (6 × 6 ml); then the aqueous acid solution was basified with ammonia (*d* 0·880) and extracted with chloroform (5 × 7 ml). The chloroform solution was washed with water, dried (Na_2SO_4) and evaporated in vacuum to dryness to give an oil. The product was purified by p.t.l.c. ($MeOH/CHCl_3/NH_3$ 10 : 90 : 1) to give a clear oil (253 mg, 68% yield) which slowly crystallized from light petroleum as pale yellow plates, m.p. 39–40° (Found: C, 78·9; H, 8·2; N, 6·2. Calc. for $C_{15}H_{19}NO$: C, 78·6; H, 8·3; N, 6·1%). The synthetic product proved identical in R_F, u.v., i.r., n.m.r. and m.s. data with natural dehydrodarlinine; it was, however, optically inactive.

Reduction of Dehydrodarlinine

A solution of synthetic dehydrodarlinine (200 mg) in aqueous methanol (30 ml, 95%) was slowly treated with $NaBH_4$ (100 mg). After the spontaneous reaction had subsided, the solution was gently refluxed for 20 min, cooled, diluted with water (60 ml), and extracted with chloroform (4 × 30 ml). The extract was washed with water, dried (Na_2SO_4) and evaporated to dryness. T.l.c. ($MeOH/CHCl_3/NH_3$ 15 : 85 : 1) on the white residue revealed two spots (R_F 0·45 and 0·30) of about equal intensity, neither of which corresponded to the starting ketone. The residue was subjected to p.t.l.c., whereupon two products were isolated.

Product 1 (89 mg), R_F 0·45, was obtained as a clear oil which slowly crystallized on standing, and upon recrystallization from ethanol formed straw-coloured rhombs, m.p. 53–54°. Its R_F, u.v., i.r., n.m.r. and m.s. data were all indistinguishable from those of natural darlinine. It was, however, optically inactive.

Product 2 (88 mg), R_F 0·30, readily formed a white solid crystalline residue which was recrystallized from ethanol to give almost colourless glassy rhombs, m.p. 58–59°. Its R_F, u.v., i.r., n.m.r. and m.s. data were all indistinguishable from those of natural epidarlinine. It was, however, optically inactive.

Natural dehydrodarlinine on reduction with $NaBH_4$ by the same procedure also gave two products in about equal proportions.

The first product was indistinguishable from reduction product 1, above, and from natural darlinine in its spectroscopic properties. It was also identical with darlinine in m.p., m.m.p. and specific rotation.

The second product was identical with natural epidarlinine in m.p., m.m.p., $[\alpha]_D$, R_F, u.v., i.r., n.m.r. and m.s. data. It was, moreover, indistinguishable from reduction product 2, above, in R_F, u.v., i.r., n.m.r. and m.s. data.

Synthesis of Dihydrodarlingianine

A solution of darlingianine (45 mg) in ethanol (3 ml) was slowly hydrogenated in the presence of 10% Pd/C (3 mg) at 19° and 1 atm until 1 mol of hydrogen was taken up. The ethanolic solution was filtered and evaporated to yield a clear oil (42 mg), which after purification by p.t.l.c. was recrystallized from ethanol to give dihydrodarlingianine, m.p. 58–60°, identical (m.p., m.m.p., R_F, u.v., i.r., n.m.r. and m.s. data) with the natural alkaloid.

Synthesis of Tetrahydrodarlingianine

A solution of darlingianine (42 mg) in ethanol (3 ml) was hydrogenated in the presence of 10% Pd/C (4 mg) at 19° and 1 atm. When the base had taken up about 2 mol of H_2, hydrogenation ceased; the ethanolic solution was filtered and evaporated to a clear oil (40 mg) which appeared homogeneous on t.l.c. The tetrahydro base had R_F, u.v., i.r., n.m.r. and m.s. data indistinguishable from those of natural tetrahydrodarlingianine.

When the reduction of darlingianine (40 mg) was carried out in ethanol (3 ml) in the presence of platinum oxide (Adams catalyst) (10 mg) at 60 p.s.i. until no more hydrogen was taken up, only one product was formed; this completely reduced tetrahydrocyclohexyl base, with R_F 0·60 (12% $MeOH/CHCl_3$), had ν_{max} (film) at 3290 cm^{-1} (hydroxy). ^1H n.m.r. δ: 4·97, br, exchangeable with D_2O, 1H, OH; 3·94, br m, 1H, CHOH; 3·55, br m, 1H, NCH; 3·13, br m, 1H, NCH; 2·37, s, 3H, NCH_3. Mass spectrum: *m/z* 266 (M).

Isomerization of Isodarlingianine to Darlingianine

A solution of isodarlingianine (18 mg) in xylene (12 ml) containing iodine (1 mg) was refluxed for 3 h. After dilution with benzene, the reaction mixture was washed with aqueous sodium thiosulfate and water, dried (Na_2SO_4), evaporated, and the product purified by p.t.l.c. to give the (*E*,*E*) isomer, darlingianine (12 mg). The isomerization was evidenced by a change in the u.v. absorption wavelength from 274 to 285 nm. The isomerized product was identical (m.p., m.m.p., R_F, u.v., i.r., n.m.r. and m.s. data) with natural darlingianine.

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