1-Phenethylisoquinoline Alkaloids. Part IV.[1,2] Isolation, Structural Elucidation, and Synthesis of c-Homoaporphines

By **Alan R. Battersby,*† Robert B. Bradbury, Richard B. Herbert, Murray H. G. Munro,** and **Robert Ramage,** The Robert Robinson Laboratories, University of Liverpool, Liverpool L69 3BX

Extraction of *Kreysigia multiflora* has yielded six alkaloids, three not having previously been found. (*RS*)-Kreysigine, (−)-floramultine, and (−)-multifloramine are shown to have the novel c-homoaporphine structures (11)—(13) by spectroscopic study and by synthesis. The (*R*)-configuration is established for (−)-multifloramine by carrying out the synthesis with resolved materials. Kreysiginone, a trace alkaloid, is shown in a similar way to be the benzo[*de*]quinoline-7-spirocyclohexadienone (21). Comment is made on the surprising stereochemical relationships among the various alkaloids.

RECENT studies [1-4] have shown that the 1-phenethylisoquinoline skeleton (1) is the central core of an important, new class of alkaloids of many types isolated from plants of the Liliaceae family. This relationship of a parent to numerous sons and daughters is reminiscent of the vast group of 1-benzylisoquinoline alkaloids found in plants of the Papaveraceae. As an example in the 1-phenethylisoquinoline series, it is now known [4] that colchicine is derived *in vivo* from (*S*)-autumnaline (2) by way of *O*-methylandrocymbine (3). The existence of (*S*)-autumnaline was first indicated by tracer experiments but later it was isolated from *Colchicum cornigerum*.[3d] At the time of these studies, it was known that morphine is biosynthesised from (*R*)-reticuline [5,6] (7) and that (+)-salutaridine [5] (8) is an important intermediate. Directly one compares (2) with (7) and (3) with (8), it is clear that parallel biosynthetic processes are operating. This suggested that an alternative mode of phenol coupling,[7] established in the 1-benzylisoquinoline series for the biosynthesis of isothebaine [8] (9) and illustrated in the Scheme, might take place on a suitable 1-phenethylisoquinoline to produce homoaporphines [based on (10)]; accordingly, compounds of this type were sought.

A phenethylisoquinoline has a C_{17} skeleton; with the advice of Professor F. Šantavý (Olomouc), whose help we gratefully acknowledge, it was found that the alkaloids [9] of *Kreysigia multiflora* Reichb. (Liliaceae) matched this requirement. A full investigation of this plant substantiated our hypothesis and allowed the homoaporphine framework (10) to be established for the three major alkaloids produced by this species.

Modification of the extraction procedure used earlier [9] on *K. multiflora* yielded the alkaloids (−)-floramultine,

† *Present address:* University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

[1] Part III, A. R. Battersby, R. B. Herbert, L. Pijewska, F. Šantavý, and P. Sedmera, *J.C.S. Perkin I*, 1972, 1736.

[2] Preliminary reports: A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450; A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *ibid.*, p. 934.

[3] (*a*) A. R. Battersby, R. B. Herbert, L. Mo, and F. Šantavý, *J. Chem. Soc.* (*C*), 1967, 1739; (*b*) A. R. Battersby, M. H. G. Munro, R. B. Bradbury, and F. Šantavý, *Chem. Comm.*, 1968, 695; J. Fredrichsons, M. F. Mackay, and A. McL. Lathieson, *Tetrahedron Letters*, 1968, 2887; N. K. Hart, S. R. Johns, J. A. Lamberton, and J. K. Saunders, *ibid.*, p. 2891; A. F. Beecham, N. K. Hart, S. R. Johns, and J. A. Lamberton, *Austral. J. Chem.*, 1968, **21**, 2829; (*c*) S. R. Johns, C. Kowala, J. A. Lamberton, A. A. Sioumis, and J. A. Wunderlich, *Chem. Comm.*, 1968, 1102; S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2219; W. Langlois, B. C. Das, P. Potier, and L. Lacombe, *Bull. Soc. chim. France*, 1970, 3535; (*d*) A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc.* (*C*), 1971, 3514.

[4] (*a*) A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J.C.S. Perkin I*, 1972, 1741; (*b*) A. C. Barker, A. R. Battersby, E. McDonald, R. Ramage, and J. H. Clements, *Chem. Comm.*, 1967, 390.

[5] D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, *J. Chem. Soc.*, 1965, 2423 and references therein.

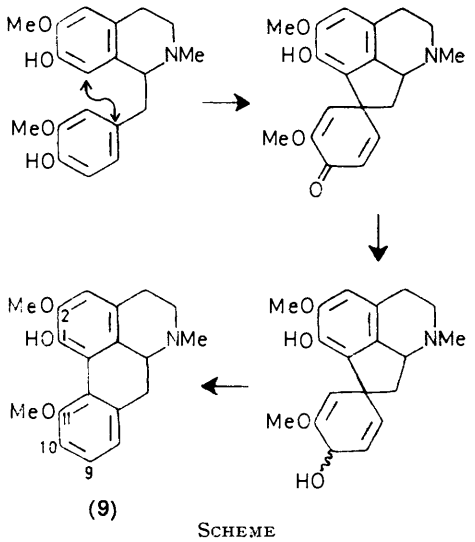
[6] A. R. Battersby, D. M. Foulkes, and R. Binks, *J. Chem. Soc.*, 1965, 3323 and references therein.

[7] D. H. R. Barton and T. Cohen, *Festschr. A. Stoll*, 1957, 117; A. R. Battersby in 'Oxidative Coupling of Phenols,' eds. A. R. Battersby and W. I. Taylor, Marcel Dekker, New York, 1967, p. 119.

[8] A. R. Battersby, T. J. Brocksom, and R. Ramage, *Chem. Comm.*, 1969, 464 and references therein.

[9] G. M. Badger and R. B. Bradbury, *J. Chem. Soc.*, 1960, 445.

(*RS*)-kreysigine, and (+)-kreysiginine previously isolated, together with a new base named (—)-multifloramine and

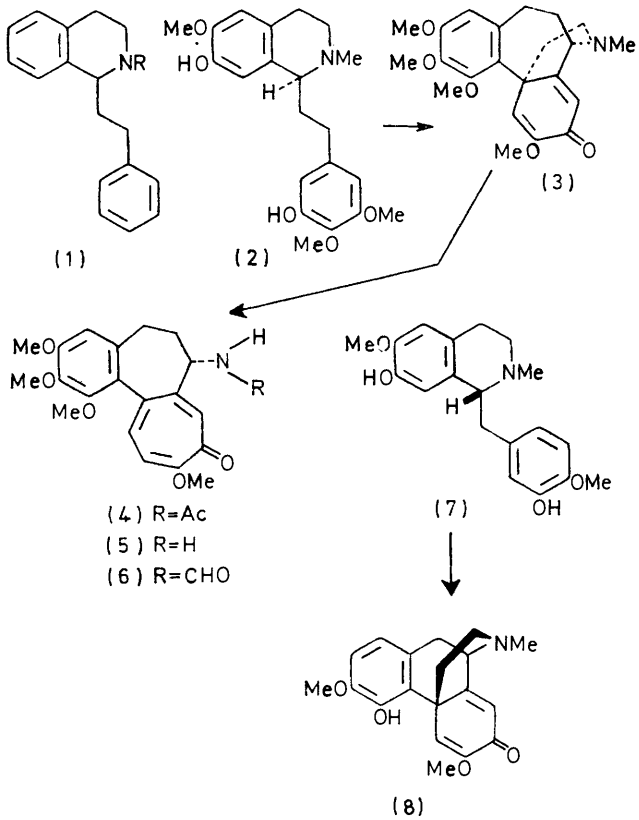


SCHEME

several minor alkaloids. Two efficient methods for separation of the crude basic material from *K. multiflora* were found to be: (*a*) partition chromatography on Celite between ethyl acetate–light petroleum (1 : 1) and pH 7 aqueous buffer, and (*b*) preliminary separation into phenolic and non-phenolic (or very weakly acidic) portions followed by further fractionation of each portion by counter-current distribution between ethyl acetate and pH 7 aqueous buffer. When the rhizomes and foliage were examined separately it was found that both contained on average *ca.* 1% of alkaloids, though the yield from foliage varied from 0·5 to 2·0% (different batches). The distribution of the various bases was also found to differ in that (*RS*)-kreysigine and (—)-floramultine were most abundant in the rhizomes whereas the foliage contained a wider spectrum of alkaloids with multifloramine as the major one. Counter-current distribution of the ' non-phenolic ' alkaloids allowed the isolation of a new dienone, kreysiginone, and deacetylcolchicine (5). Colchicine (4) and *N*-formyldeacetylcolchicine (6) have also been found [10] in *K. multiflora* and the occurrence of the tropolones (4)—(6) is of considerable interest; this will be brought out in the following paper [11] where biosynthetic studies on the homoaporphines are described.

Methylation of multifloramine and floramultine with diazomethane gave in each case a mixture of kreysigine and *O*-methylkreysigine; the latter was formed from kreysigine by extended treatment with diazomethane. In this way, the three alkaloids were immediately shown to be closely related; the structural argument best starts with kreysigine, $C_{22}H_{27}NO_5$ (confirmed by mass spectrometry). Analysis of the n.m.r. spectrum showed that one *N*-methyl and four *O*-methyl groups are present together with two aromatic protons giving rise to *singlets* at τ 3·41 and 3·46. The region τ 6·5—8·1 contained unresolved signals corresponding to nine protons. Confirmation that the fifth oxygen atom occurs in a phenolic hydroxy-group came from the i.r. and u.v. spectra; the latter underwent a bathochromic shift in alkaline solution. These data and arithmetic show that the parent skeleton of kreysigine (all functional groups replaced by hydrogen atoms) has the composition $C_{17}H_{17}N$ and contains two aromatic rings; it is therefore tetracyclic, corresponding exactly to a didehydro derivative of 1-phenethylisoquinoline [*e.g.* (10)].

The u.v. spectrum of kreysigine indicated significant conjugation of the two aromatic nuclei and so supported the homoaporphine structure. In addition, one methoxy-group was shielded (τ 6·41) relative to the others

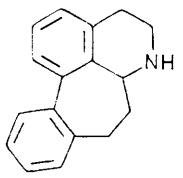


(two at τ 6·14 and one at 6·17). This phenomenon is well known in the aporphine series [12] where a methoxy-group at C-1 or C-11 [see (9)] of the twisted biphenyl system is shielded by the adjacent aromatic ring. Accordingly, structure (11) was proposed for (*RS*)-kreysigine; the oxygenation and methylation patterns were largely selected on biogenetic grounds with the structure of autumnaline (2), the precursor of the *Colchicum* alkaloids,[4] in mind.

(—)-Multifloramine, $C_{21}H_{25}NO_5$, and (—)-floramultine, also $C_{21}H_{25}NO_5$ (the earlier molecular formula [9] was revised in the light of mass spectral data), are both de-*O*-methyl derivatives of kreysigine; this follows from

[10] F. Šantavý, *Experientia*, 1967, **23**, 273.
[11] A. R. Battersby, P. Böhler, M. H. G. Munro, and R. Ramage, following paper.
[12] *E.g.* W. H. Baaschers, R. R. Arndt, K. Pachler, J. A. Weisbach, and B. Douglas, *J. Chem. Soc.*, 1964, 4778.

the molecular formulae and the *O*-methylation studies mentioned earlier. Both show one *O*-methyl signal at high field in their n.m.r. spectra. In addition, *OO*-diacetylfloramultine on partial hydrolysis yielded a mono-*O*-acetyl derivative which by *O*-methylation and subsequent hydrolysis yielded (—)-kreysigine. So on the basis of structure (11) for kreysigine, the tentative structures (12) and (13) were assigned to (—)-multifloramine and (—)-floramultine, not necessarily respectively.



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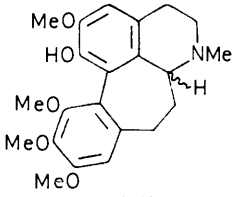

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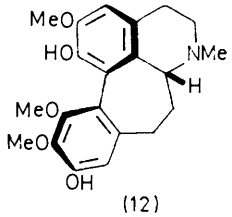

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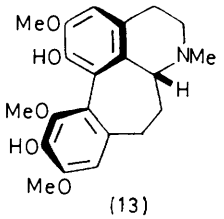

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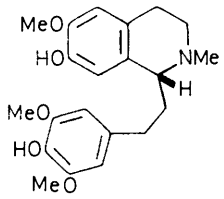

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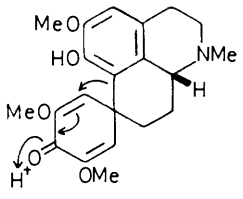

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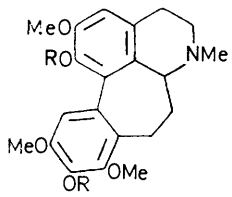
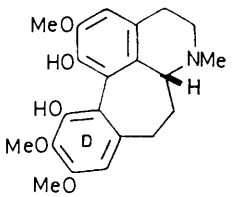


(16) R=Ac
(17) R=H



(18)

Scarcity of the natural materials precluded extensive degradations and the structural problem was solved by the synthetic approach. The selected route was based on the known synthetic and biosynthetic relationships in the 1-benzylisoquinoline series depicted in the Scheme.

The (*RS*)-diphenol [as (14)], synthesised as in earlier work,[4a] was oxidised by alkaline ferricyanide to yield the racemic dienone [as (15)] in the high yield of 49%. This product exhibited i.r. maxima at 3550, 1660, and 1621 cm^{-1} and n.m.r. signals consistent with the structure at τ 7·60 (*N*-Me), 6·50, 6·43, and 6·29 (*O*-Me), 4·22 and 4·07 (each *J* 2 Hz, olefinic H), and 3·54 (aromatic H). The small coupling of the olefinic signals arises from transannular interaction.[13] Dienone–phenol rearrangement involving aryl migration was effected by concentrated sulphuric acid to yield (*RS*)-multifloramine [as (13)] identical with the natural product except for optical activity. In view of the *O*-methylation studies described above, this also constitutes a formal synthesis of (*RS*)-kreysigine. Though a complete study was not carried out, there is good evidence for the alternative alkyl migration having occurred in the dienone–phenol rearrangement when acetic anhydride–sulphuric acid was used. In this case, the rearrangement must proceed from the *O*-acetyl dienone in which the migratory aptitude of the aryl group would be expected to be decreased relative to that of the free phenol. The n.m.r. spectrum of the *O*,*O*-diacetate so produced showed the absence of a shielded methoxy-group of the type discussed already in relation to kreysigine; the spectrum is, however, consistent with structure (16). Also, the diphenol (17) isolated after hydrolysis was spectroscopically distinguishable from multifloramine (13).

Resolution of the *OO*-diacetate of the base (14 and enantiomer) with the (*RR*)- and (*SS*)-forms of *OO*-ditoluoyltartaric acid followed by hydrolysis gave the two enantiomers of the diphenol (14), isolated as the hydrochloride salts. The (—)-hydrochloride was carried through the sequence of phenol coupling and dienone–phenol rearrangement and the product was identical with natural (—)-multifloramine. The absolute configuration of (*S*)-autumnaline (2) had been established in earlier work [4b] by o.r.d. measurements and its hydrochloride is dextrorotatory [conditions of measurement identical with those used for the (—)-hydrochloride above]. Since autumnaline differs from the diphenol (14) only by the interchange of two nuclear substituents at a site remote from the chiral centre, the absolute *R*-configuration (14) can be assigned to the base yielding the laevorotatory hydrochloride. It follows that (—)-multifloramine has the *R*-configuration illustrated in structure (13) in agreement with research carried out simultaneously elsewhere and referred to below.

As a consequence of structure (13) being settled for (—)-multifloramine, (—)-floramultine has the structure (12); our only evidence for the absolute configuration in this case is comparison with (—)-multifloramine (see later). Further, (*RS*)-kreysigine, which is so weakly acidic that it is very difficult to extract from organic solvents into alkali, can be confirmed as having structure (11). In this, the phenolic hydroxy-group is severely hindered in the twisted biphenyl system. The partial methylation work and acetylation–deacetylation studies already outlined are also in clear support of the assigned position for the phenolic hydroxy-group in (*RS*)-kreysigine (11).

It is of interest that alkaloid CC-24 from *Colchicum cornigerum* has been shown [3d] to have structure (18),

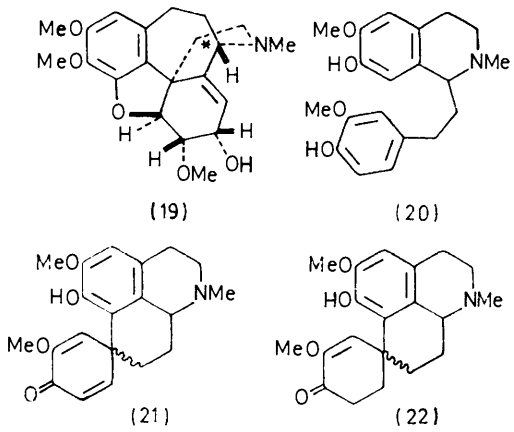
[13] W. von Philipsborn, Habilitationsschrift, University of Zurich, 1962; see also A. R. Battersby, J. H. Clements, and T. H. Brown, *J. Chem. Soc.*, 1965, 4550; and L. J. Haynes, K. L. Stuart, D. H. R. Barton, and G. W. Kirby, *J. Chem. Soc.* (*C*), 1966, 1676.

representing the only remaining monophenolic variation on ring D.

Our preliminary communication [2] stimulated interest in this area by other researchers. Thus, it was shown [14] by c.d. measurements that (−)-floramultine (12) belongs to the *R*-series. Also, Brossi and his co-workers [15] applied our synthetic sequence in both *R*- and *S*-series to establish independently the absolute configuration (13) for (−)-multifloramine. Finally, Kametani's group has carried out extensive synthetic work on structures derivable by oxidative coupling of 1-phenethylisoquinolines, or by related processes.[16]

The stereochemistry of the alkaloids from *Kreysigia multiflora* has surprising features. Kreysigine (11) is completely racemic yet its close relatives (−)-multifloramine (13) and (−)-floramultine (12) are optically active with the *R*-configuration. In contrast, the co-occurring base (+)-kreysiginine has the *S*-configuration at the corresponding chiral centre marked with an asterisk on structure (19); this also represents the absolute configuration.[3b] In biosynthetic terms, structure (19) is closely related to the homoaporphines (11)—(13). The foregoing facts emphasise the impressive stereochemical selectivity of the plant's biosynthetic activities.

The spectroscopic data of the very minor alkaloid kreysiginone indicated that it might have a structure of type (21). Accordingly, the diphenol [4a] (20) was oxidised with alkaline ferricyanide to afford a separable mixture



of two diastereoisomeric dienones (21) differing in configuration at the spiro-centre; they will be called dienone-I (transition at 155°, m.p. 194°) and dienone-II (m.p. 202°). All the spectroscopic data for both dienones were consistent with structure (21) and dienone-I was found to be identical, apart from optical activity, with kreysiginone. Accompanying kreysiginone in the plants, and separable from it with difficulty, was a trace of an alkaloid with spectroscopic properties corresponding to the dihydrokreysiginone structure (22). The amount available was too small for rigorous work. However, such a co-occurrence of a cross-conjugated dienone and the corresponding enone has been met before in *P. orientale*.[17]

Oxidative conversion of base (20) into the two dienones has been carried out independently by Kametani *et al.*[18]

The novel structures of the alkaloids of *K. multiflora* and their unusual stereochemical relations heightened interest in their biosynthesis; tracer studies in these plants on the homoaporphine system are described in the following paper.[11]

EXPERIMENTAL

General directions are given in ref. 19. In several cases, it was necessary to measure specific rotations on small samples; for these, correspondingly large error limits are recorded.

Extraction of Kreysigia multiflora.—The dry plant material was separated into rhizomes (761 g) and foliage (1435 g). All batches were ground to powders which were extracted at 20° first with ethanol (10 l) and then with 1% citric acid in 1 : 1 water–ethanol (20 l); the two extracts were treated separately as follows. The solvent was evaporated off and the residue was partitioned between water and chloroform (1 l of each). After the aqueous phase had been basified with potassium carbonate, it was extracted thrice with chloroform (solution A). The original chloroformic layer was extracted several times with 2N-sulphuric acid (filter emulsions), and the acidic solution was basified and extracted with chloroform (solution B). The residue from evaporation of the aqueous ethanolic citric acid extract was dissolved in water, filtered, basified with potassium carbonate and extracted thrice with chloroform (solution C). Evaporation of the combined solutions A—C yielded crude alkaloid, 7·4 g from rhizomes and 7·2 g from foliage. Where separation of phenols from non-phenols (or weakly acidic phenols) was carried out, it was done by partition between chloroform and N-sodium hydroxide in the usual way.

Isolation of the Alkaloids.—(a) *By partition chromatography.* The column was prepared from Celite (500 g) impregnated with phosphate–citrate buffer (250 ml) which had previously been equilibrated with the organic eluting phase [1 : 1 v/v ethyl acetate–light petroleum (b.p. 60—80°)]. The buffer was a mixture of 0·1M-citric acid and 0·2M-disodium hydrogen phosphate (3·53 : 16·47 v/v). The alkaloids (3·15 g) from rhizomes gave the following in order of elution: (*RS*)-kreysigine (110 mg), (−)-floramultine (1·24 g), and a mixture of floramultine, kreysiginone, and deacetylcolchicine.

The foliage bases (4·53 g) similarly gave (*RS*)-kreysigine (160 mg), (−)-floramultine (950 mg), and a fraction containing more polar alkaloids. Rechromatography of the latter afforded (−)-multifloramine (435 mg), which moved more slowly than floramultine.

(b) *By counter-current distribution.* The phenolic alkaloids (2·2 g) were partitioned (10 ml phases) between ethyl acetate and the same pH 7 buffer used in (a). After 90

[14] A. F. Beecham, N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.*, 1968, **21**, 2829.

[15] A. Brossi, J. O'Brien, and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 678.

[16] *Inter alia* T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Org. Chem.*, 1968, **33**, 690; *J. Chem. Soc.* (*C*), 1970, 382; T. Kametani, T. Sugahara, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. Comm.*, 1971, 724; T. Kametani, Y. Satoh, and K. Fukumoto, *J.C.S. Perkin I*, 1972, 2160 and references therein.

[17] A. R. Battersby and T. H. Brown, *Chem. Comm.*, 1966, 170.

[18] T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1968, 1003 and references therein.

[19] A. R. Battersby, E. S. Hall, and R. Southgate, *J. Chem. Soc.* (*C*), 1969, 721.

transfers, a good separation of the following had been achieved (partition ratio, K, is quoted): (*RS*)-kreysigine (170 mg; K 1·25), (−)-floramultine (500 mg, K 0·56); (−)-multifloramine (113 mg, K 0·37), and (+)-kreysiginine (267 mg; K 0·17). The last appears in the ' phenolic ' fraction.

Similar partition of the ' non-phenolic ' alkaloids (805 mg) allowed the separation of a fraction rich in kreysiginone. P.l.c. of this on silica (10% methanol in chloroform) afforded kreysiginone and dihydrokreysiginone in admixture and pure deacetylcolchicine, which was identified by full spectroscopic and chromatographic comparison with authentic material. Dihydrokreysiginone was separated from kreysiginone by crystallisation from ethyl acetate; p.l.c. as before of the material in the mother liquors gave pure kreysiginone.

Physical Data for the Isolated Alkaloids.—(*RS*)-Kreysigine (11) (2,9,10,11-tetramethoxy-c-homo-6αβ-aporphin-1-ol): m.p. 187—189° (from ethanol); $\nu_{max.}$ (CCl_4) 3500, 3400, 1600, and 1128 cm^{-1}; $\lambda_{max.}$ 221 (53,900), 260 (15,600), and 293 nm (6600), shifted in base to 321 nm; τ 3·41 (1H, s, ArH) 3·44 (1H, s, ArH), 6·14 (3H, OMe), 6·17 (3H, OMe), 6·41 (3H, OMe), and 7·64 (3H, NMe); *m/e* 385 (M^+, 50%), 370 (24), and 368 (100).

(−)-Floramultine (12) (2,10,11-trimethoxy-c-homo-6αβ-aporphine-1,9-diol): m.p. 230—231° (from ethanol), $[\alpha]_D$ −77° ± 3° ($CHCl_3$); $\nu_{max.}$ ($CHCl_3$) 3550, 3400, 1600, and 1120 cm^{-1}; $\lambda_{max.}$ 225 (45,100), 258 (13,400), and 295 (6500) nm, shifted in base to 286 nm; τ 3·46 (1H, s, ArH), 3·41 (1H, s, ArH), 6·11 (3H, OMe), 6·16 (3H, OMe), 6·45 (3H, OMe), and 7·70 (3H, NMe); *m/e* 371 (M^+, 56%), 356 (33), and 354 (100).

(−)-*Multifloramine* (13) (2,9,11-*trimethoxy*-c-*homo*-6αβ-*aporphine*-1,10-*diol*): m.p. 209—212° (from ethanol) (Found: C, 67·2; H, 6·9. $C_{21}H_{23}NO_5$,0·5EtOH requires C, 67·0; H, 7·1%), $[\alpha]_D^{23}$ −108° ± 3° ($CHCl_3$); $\nu_{max.}$ (CCl_4) 3560, 1618, 1488, and 1124 cm^{-1}; $\lambda_{max.}$ 221 (22,000) 261, (5560), and 295 nm (3710), shifted in base to 318 nm (5350); τ 3·38 (1H, s, ArH), 3·45 (1H, s, ArH), 6·13 (6H, OMe), 6·46 (3H, OMe), and 7·74 (3H, NMe); *m/e* 371 (M^+, 50%) and 354 (100).

Kreysiginone (21) (1,2,3,8,9,9a-hexahydro-6-hydroxy-3′,5-dimethoxy-1-methyl-7*H*-benzo[*de*]quinoline-7-spiro-cyclohexa-2′,5′-dien-4′-one): m.p. 193—194° (from benzene); $\nu_{max.}$ ($CHCl_3$) 3500, 1659, 1633, and 1614 cm^{-1}; $\lambda_{max.}$ 214 (34,000), 243infl (14,200), and 287 (6000) nm; *m/e* 341 (M^+); identified by direct comparison with synthetic material (see later).

Dihydrokreysiginone (?): m.p. 217—222° (from benzene); $\nu_{max.}$ ($CHCl_3$) 3500, 1678, 1635, and 1610 cm^{-1}; $\lambda_{max.}$ 220 and 269 nm, shifted in base to 288 nm; τ 3·46 (1H, s, ArH), 4·26 (1H, olefinic), 6·16 (3H, OMe), 6·46 (3H, OMe), and 7·43 (3H, NMe).

Conversion of (−)-*Floramultine into* (−)-*Kreysigine.*—A solution of (−)-floramultine (95 mg) in pyridine (1 ml) and acetic anhydride (1 ml) was kept at 20° for 1 day and then evaporated to give *OO*-diacetylfloramultine, homogeneous by t.l.c., $\nu_{max.}$ 1760 and 1610 cm^{-1}; τ 3·24 and 3·32 (each 1H, s, ArH), 6·18, 6·22, and 6·56 (each 3H, OMe), 7·61 (3H, NMe), and 7·72 and 7·97 (each 3H, Ac); *m/e* 455 (M^+, 10%), 412 (20), 396 (100), and 354 (15).

2N-Sodium hydroxide (1 drop) was added at 20° to a solution of the above diacetate in methanol (4 ml). After 16 h, the solvent was evaporated off and the residue was extracted with chloroform to yield mono-*O*-acetylfloramultine, homogeneous by t.l.c., $\nu_{max.}$ 3520 and 1750 cm^{-1}; 3·28 and 3·48 (each 1H, s, ArH), 6·10, 6·21, and 6·58 (each 3H, OMe), 7·64 (3H, NMe), and 7·97 (3H, Ac); *m/e* 413 (M^+, 14%), 398 (5), 370 (22), 354 (100), and 338 (11).

The monoacetate was treated in methanol with an excess of diazomethane for 2 days and the product from evaporation was hydrolysed as above with an excess of 2N-sodium hydroxide in methanol. Recovery of the basic product as usual afforded (−)-kreysigine, identical, apart from optical activity, with (*RS*)-kreysigine by full spectroscopic and chromatographic comparison, $[\alpha]_D$ −59° ± 10° ($CHCl_3$).

O-*Methylation of* (−)-*Floramultine* (12) *and* (−)-*Multifloramine* (13).—(−)-Floramultine (83 mg) in methanol was treated at 4° with an excess of diazomethane for 2 days. Chromatography of the product on activity IV alumina (elution with benzene–ethyl acetate mixtures) gave *OO*-dimethylfloramultine (20 mg) and the mono-*O*-methyl ether (37 mg), m.p. 108—110° (from propan-2-ol). The latter was identical with the foregoing product and was further identified by t.l.c. and i.r. comparison with (*RS*)-kreysigine.

The dimethyl ether was further purified by p.l.c. on silica with 10% methanol in chloroform to yield a homogeneous gum, $\nu_{max.}$ 1598, 1470, and 1120 cm^{-1}; τ 3·27 and 3·50 (each 1H, s, ArH), 6·14 (9H, OMe), 6·41 (3H, OMe), 6·50 (3H, OMe), and 7·62 (NMe). It yielded a crystalline *hydrobromide*, m.p. 243° (decomp.) (Found: C,56·3; H, 6·3; OMe, 32·0. $C_{23}H_{30}BrNO_5$,0·5H_2O requires C, 56·5; H, 5·95; OMe, 32·7%).

Methylation of (−)-multifloramine under the same conditions gave the same two products, identified by comparison with those above.

Resolution of the 1-*Phenethylisoquinoline* [*as* (14)].—A solution of the racemic diphenolic base [4a] (3·1 g) in AnalaR chloroform (20 ml) was stirred vigorously for 0·5 h at 20° with anhydrous sodium carbonate (4 g) and acetic anhydride (5 ml). Water (10 ml) and sodium carbonate (1 g) were then added and the organic layer was washed, dried, and evaporated to yield the *OO*-diacetate as a gum, homogeneous by t.l.c.; $\nu_{max.}$ 1755 and 1600 cm^{-1}.

This total product in warm methanol (10 ml) was treated with *OO*-ditoluoyl-L-tartaric acid (3 g). The salt which gradually separated was collected (1·96 g) and the mother liquors were evaporated to allow recovery of the *OO*-diacetyl base by partition between chloroform and aqueous sodium carbonate. This product (2·2 g) was treated in warm methanol (6 ml) with *OO*-ditoluoyl-D-tartaric acid (2 g) to yield crystalline salt (2·02 g). Both salts so obtained were recrystallised twice from methanol; the rotation of the salt at this point was the same as after five recrystallisations.

The *OO*-ditoluoyl-L-tartrate salt (1·56 g) of the (*S*)-base showed m.p. 177—178° (decomp.), $[\alpha]_D^{20}$ +40·5° ± 2° ($CHCl_3$).

The *OO*-ditoluoyl-D-tartrate salt (1·38 g) of the (*R*)-base showed m.p. 178—179° (decomp.), $[\alpha]_D^{20}$ −39° ± 2° ($CHCl_3$).

2N-Sodium hydroxide (3 ml) was added to the foregoing salt (732 mg) of the (*R*)-base in methanol (10 ml) and the solution was first warmed and then left at 20° for 2 h. After addition of water (70 ml), the mixture was acidified with 2N-hydrochloric acid, then basified with sodium hydrogen carbonate, and finally extracted with chloroform. Concentrated hydrochloric acid (1 drop) was added to the chloroformic solution followed by methanol (5 ml) and the solvents were evaporated off to leave the (*R*)-base hydrochloride (444 mg), $[\alpha]_D^{26}$ −30·5° ± 2° (in MeOH).

Synthesis of Racemic and Optically Active Dienone [*as* (15)].

—The (*RS*)-diphenol hydrochloride [as (14)] (0·93 g) was shaken with a mixture of AnalaR chloroform (40 ml) and *freshly prepared saturated* aqueous sodium hydrogen carbonate (20 ml) until a solution was obtained. Freshly ground potassium ferricyanide (1·495 g) was added and the mixture was shaken for 1 h. The separated aqueous layer was extracted four times with chloroform; these extracts were added to the main chloroformic solution and the whole was evaporated. The residue was fractionated on activity IV alumina (40 g) in 3 : 7 (v/v) chloroform–benzene to yield the racemic 1,2,3,8,9,9a-*hexahydro*-6-*hydroxy*-3,5,5′-*trimethoxy*-1-*methyl*-7H-*benzo*[de]*quinoline*-7-*spirocyclohexa*-2′,5′-*dien*-4′-*one* (375 mg), m.p. 176—178° (from ethyl acetate) (Found: C, 66·25; H, 7·0. $C_{21}H_{25}NO_5$,0·5EtOAc requires C, 66·5; H, 7·0%); $\nu_{max.}$ ($CHCl_3$) 3550, 1660, and 1621 cm^{-1} (and 1725 cm^{-1} from EtOAc of crystallisation); $\lambda_{max.}$ 227 (40,000) and 278 nm (13,000); τ 3·54 (1H, s, ArH), 4·07 and 4·22 (each 1H, d, *J* 2 Hz, olefinic), 6·29, 6·43, and 6·50 (each 3H, OMe), and 7·60 (3H, NMe) (signals also from EtOAc); *m/e* 371 (M^+), 370, 366, and 349 (100%).

Repetition of the foregoing sequence on the (*R*)-diphenol (14) gave the (−)-dienone, $[\alpha]_D^{24}$ −54° ± 4° (in MeOH).

Synthesis of Racemic and of (−)- and (+)-*Multifloramine*. —A solution of the racemic dienone (234 mg) in concentrated sulphuric acid (6 ml) was kept at 20° for 16 h, then was mixed with ice (20 g), adjusted to pH *ca.* 3 with 2N-sodium hydroxide, and basified with sodium hydrogen carbonate. Extraction with chloroform gave a gum (196 mg), which was filtered in chloroform through a short column of activity IV alumina, and the product was purified by p.l.c. on silica. (RS)-*Multifloramine* crystallised from ethanol [m.p. 190—192° (decomp.)] and was identical, apart from optical activity, with the natural alkaloid (i.r., u.v., n.m.r., and mass spectrometric and t.l.c. comparison) (Found: C, 68·1; H, 6·6. $C_{21}H_{25}NO_5$ requires C, 67·9; H, 6·8%).

Repetition of the above rearrangement using (−)-dienone (15) gave (−)-multifloramine, m.p. 214—216° (from ethanol), $[\alpha]_D$ −98° ± 10°, indistinguishable from the natural alkaloid.

A small quantity of (+)-multifloramine was prepared by the foregoing sequence for study of its c.d. behaviour (*cf.* ref. 15); the measurements were kindly made by Professor W. Klyne and Dr. M. Scopes (Westfield College): (+)-multifloramine (in methanol): λ (Δε) 299 (−7·85m), 259 (−19·6m), 231 (−3·27m), and 208 (+47·0!); (−)-multifloramine (in methanol): λ (Δε) 299 (+8·2m), 258 (+20·0m), 229 (+4·25m), and 215 (−44·3!).

Synthesis of Racemic Kreysiginone and of Dienone-II.— The diphenol [4a] (20) (3·18 g) was distributed between chloroform (60 ml) and freshly prepared saturated sodium hydrogen carbonate solution (30 ml) then potassium ferricyanide (6·32 g) was added. After being shaken for 1 h, the chloroformic solution was separated and the aqueous layer was extracted with chloroform (3 × 20 ml). The combined extracts were washed with water, dried, and evaporated to give a gum (2·1 g) which was chromatographed on activity IV alumina. Elution with 35% chloroform in benzene gave a mixture (1·25 g) of dienones and starting material. The phenols were removed by extraction of a chloroformic solution with 2N-sodium hydroxide to give the two dienones (0·965 g), which on crystallisation from benzene–methylene chloride and then from acetonitrile–ether afforded dienone-I (311 mg), m.p. 193—194° (transition at 155°). Dienone-II (435 mg), m.p. 200—202°, separated on concentration of the mother liquors and was purified by further recrystallisation from acetonitrile–ether. *Dienone*-I was shown by full spectroscopic and t.l.c. comparison to be identical, apart from optical activity, with natural kreysiginone. It showed $\nu_{max.}$ 3550, 1659, 1633, and 1614 cm^{-1}; $\lambda_{max.}$ 214 (34,000), 243infl (14,200), and 287 nm (6000); *m/e* 341 (M^+); τ 3·48 (1H, s, ArH), 4·05 and 3·72 (each 1H, d, *J* 10 Hz, olefinic), 3·17 (1H, dd, *J* 3 and 10 Hz, olefinic), 6·24 (3H, OMe), 6·46 (3H, OMe), and 7·55 (3H, NMe) (Found: M^+, 341·1606. $C_{20}H_{23}NO_2$ requires *M*, 341·1627). *Dienone*-II showed $\nu_{max.}$ 3500, 1661, 1635, and 1609 cm^{-1}; $\lambda_{max.}$ 215 (34,400), 243infl (13,000), and 287 nm (5900); *m/e* 341 (M^+) and 312 (100%); τ 3·49 (1H, s, ArH), 4·23 and 3·80 (each 1H, d, *J* 10 Hz, olefinic), 3·04 (1H, dd, *J* 3 and 10 Hz, olefinic), 6·26 (3H, OMe), 6·41 (3H, OMe), and 7·59 (3H, NMe) (Found: C, 69·7; H, 7·0; N, 4·25%; M^+, 341·1603. $C_{20}H_{23}NO_2$ requires C, 70·35; H, 6·8; N, 4·1%; *M*, 341·1627).

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