Importance of Steric Factors in the Conversion of Proaporphines into Aporphines. Stereochemistry of the Dienone–Phenol and Dienol–Benzene Rearrangements

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Proaporphines belonging to the C-6a-(*R*) configuration will undergo counter-clockwise rotation of the dienone system during their acid-catalysed rearrangement to aporphines, while proaporphines of the (*S*) configuration will suffer a corresponding clockwise rotation; the aryl ring thus migrates from the C-13 spiro-centre to that carbon of the dienone which is *syn* to 6a-H.

Various studies of *Berberis* species of northern Pakistan have resulted in the past in the characterization of the sole proaporphine–benzylisoquinoline dimer hitherto known, (+)-pakistanamine (**1**)[1] (whose stereochemistry at the C-13 proaporphine spiro-centre had not been established prior to the present study) as well as of five aporphine-benzylisoquinolines, (+)-1-*O*-methylpakistanine (**6**), (+)-pakistanine (**7**), (+)-chitraline (**8**), (−)-khyberine (**12**), and (−)-kalashine (**13**).[2]

A preliminary examination of two Chilean barberries, *Berberis valdiviana* Phil. and *B. empetrifolia* Lam. led to the isolation of four new amorphous phenolic proaporphine–benzylisoquinolines, namely (+)-valdivianine (**2**), (+)-valdiberine (**3**), (+)-patagonine (**4**), and (+)-berbivaldine (**5**).‡§

Each of the new dimers (**2**)—(**5**) rearranged in dilute hydrochloric acid to its aporphine–benzylisoquinoline analogue, in a manner similar to the known conversion of (+)-pakistanamine (**1**) into (+)-1-*O*-methylpakistanine (**6**).[1] (+)-Valdivianine (**2**) thus gave (+)-pakistanine (**7**), and (+)-valdiberine (**3**) led to (+)-chitraline (**8**). Rearrangement of (+)-patagonine (**4**) furnished (+)-(**9**)¶ which has not so far been isolated from a plant source. Significantly, rearrangement of (+)-berbivaldine (**5**) supplied the hitherto unknown (+)-porveniramine (**10**)¶ which we have now also found as a new natural product in *B. empetrifolia*.§ As further structural proof, it was established that diazomethane *O*-methylation of (+)-porveniramine (**10**) provides (+)-1,10-di-*O*-methylpakistanine which had previously been prepared by *O*-methylation of (+)-pakistanine (**7**).[1]

Proton nuclear Overhauser enhancements (n.o.e's) were used to solve the stereochemistry of alkaloids (**1**)—(**5**) at the C-13 spiro-centre. The chemical shifts for 6a-H (δ 3.41, J_1 6.1 Hz, J_2 10 Hz), 7β-H (δ 2.45, J_1 6.1 Hz, J_2 12 Hz), and 7α-H (δ 2.16, J_1 10.4 Hz, J_2 12 Hz) in pakistanamine (**1**) were first assigned by decoupling experiments.

Irradiation of 6a-H (δ 3.41) in pakistanamine then gave signal enhancements of 9% for 12-H (δ 7.05) and 4% for 7β-H (δ 2.45). When 7α-H (δ 2.16) was irradiated, 7β-H (δ 2.45) and

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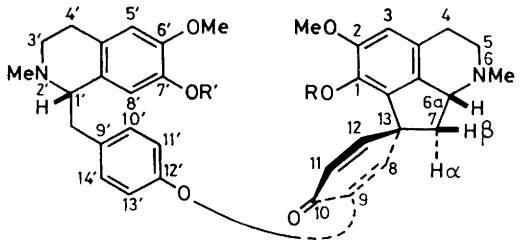
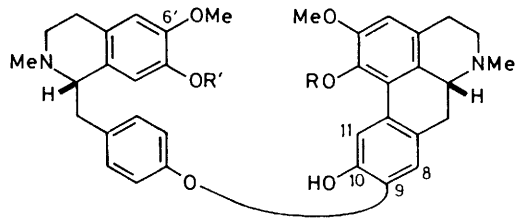
‡ (+)-Valdivianine (**2**), $C_{37}H_{40}N_2O_6$, $[\alpha]_D^{25}$ +120° (*c* 0.2, MeOH), c.d. Δε(nm)(MeOH) −0.7(300), +8.0(278), +3.8(235), and +17(211): 1-*O*-acetylvaldivianine, $C_{39}H_{42}N_2O_7$, c.d. Δε(nm) (MeOH) +9.2(276), +5.3(249), and +19(229); (+)-valdiberine (**3**), $C_{36}H_{38}N_2O_6$, λ_{max} (MeOH) 212, 231, and 284 nm (log ε 4.71, 4.57, and 4.02), $[\alpha]_D^{25}$ +91° (*c* 0.4, MeOH), c.d. Δε(nm)(MeOH) −0.6(300), +10(277), +5.1(339), and +14(230): 1,7′-di-*O*-acetylvaldiberine, $C_{40}H_{42}N_2O_8$, c.d. Δε(nm) (MeOH) +8.5(276), −0.5(248), and +21(229). Valdiberine has been suggested to be a biogenetic intermediate between berbamunine, on the one hand, and chitraline and kalashine on the other, see ref. 2: (+)-patagonine (**4**), $C_{37}H_{40}N_2O_6$, $[\alpha]_D^{25}$ +192° (*c*. 0.2, MeOH), c.d. Δε(nm) (MeOH) 8.8(279), +5.5(248), and +32(230): 7′-*O*-acetylpatagonine, $C_{39}H_{42}N_2O_7$, c.d. Δε(nm) (MeOH) +8.7(273), 0(248), and +14(232); berbivaldine (**5**), $C_{36}H_{38}N_2O_6$, $[\alpha]_D^{25}$ +140° (*c* 0.4, MeOH), c.d. Δε(nm) (MeOH) −0.5(302), +6.4(278), +2.4(242), and +12(212): 1,6′-di-*O*-acetylberbivaldine, $C_{40}H_{42}N_2O_8$, c.d. Δε (nm) (MeOH) +8.7(276), −0.2(249), and +16(229).

§ A total of 10 kg of dried *B. valdiviana* gave (**1**) (3 mg), (**2**) (70 mg), (**3**) (15 mg), (**4**) (3 mg), (**5**) (7 mg), (**7**) (15 mg), (**8**) (5 mg), and (**11**) (1 mg). *B. empetrifolia* (20 kg, dried) furnished (**2**) (50 mg), (**4**) (190 mg), (**6**) (5 mg), (**8**) (34 mg), and (**10**) (51 mg).

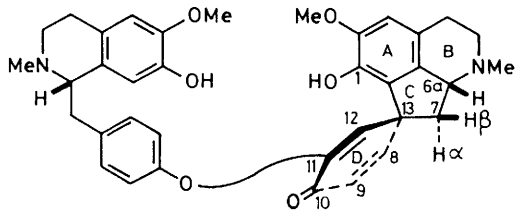
¶ Dimer (**9**), $C_{37}H_{40}N_2O_6$, ^{1}H n.m.r. δ 2.50 (6H, s), 3.71 (3H, s), 3.85 (3H, s), 3.88 (3H, s), 6.35 (1H, s), 6.53 (1H, s), 6.61 (1H, s), 6.72 (1H, s), 6.97 and 7.10 (4H, dd, J_0 8.5 Hz), and 8.10 (1H, s), $[\alpha]_D^{25}$ +29° (*c*. 0.4, MeOH), c.d. Δε(nm)(MeOH) +2.6(304), +7.2(275), −33(239), and +27(210); (+)-porveniramine (**10**), $C_{36}H_{38}N_2O_6$, ^{1}H n.m.r. δ 2.50 (3H, s), 2.52 (3H, s), 3.51 (3H, s), 3.85 (3H, s), 5.90 (1H, s), 6.53 (1H, s), 6.55 (1H, s), 6.69 (1H, s), 8.07 (1H, s), and 6.89 and 6.99 (4H, dd, J_0 8.8 Hz), $[\alpha]_D^{25}$ +40° (*c* 0.1, MeOH), c.d. Δε(nm) (MeOH) +5.4(305, +8.2(274), −24 (244), and +22(212); (+)-epivaldiberine (**11**), $C_{36}H_{38}N_2O_6$, λ_{max} (MeOH) 210, 232 sh, and 284 nm (log ε 4.65, 4.47, and 3.86), $[\alpha]_D^{25}$ +31° (*c* 0.1, MeOH), c.d. Δε(nm) (MeOH) +2.3(300), +3.7(277), −5.2(246), and +8.7(212).



(1) R = R' = Me
(2) R = H, R' = Me
(3) R = R' = H
(4) R = Me, R' = H
(5) as (2), but with 6'-OH instead of 6'-OMe



(6) R = R' = Me
(7) R = H, R' = Me
(8) R = R' = H
(9) R = Me, R' = H
(10) as (7), but with 6'-OH instead of 6'-OMe



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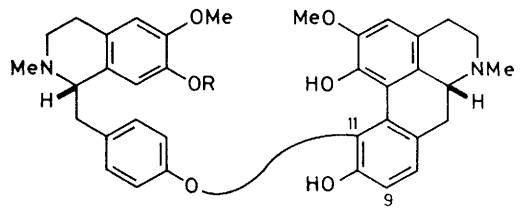


(12) R = H
(13) R = Me

Table 1. ^{1}H N.m.r. chemical shifts (δ, 360 MHz, $CDCl_3$) for the proaporphine–benzylisoquinolines.[a]

Compound	NCH_3		OCH_3			arom-H					CH_2=C*H*–		
	N-2'	N-6	C-2	C-6'	C-7'	3-H	5'-H	8'-H	10',14'-H	11',13'-H	8-H[c]	11-H[d]	12-H[e]
(1)	2.35	2.52	3.80	3.84	3.52	6.56	6.61	5.95	7.01br.	7.01br.	6.15	6.35	7.05
(2)	2.36	2.54	3.83	3.83	3.54	6.55	6.57	5.99	7.01	7.01	6.19	6.34	6.99
(3)	2.36	2.50	3.80	3.80	—	6.50	6.54	5.66	7.00	7.00	6.03	6.37	6.99
(4)	2.37	2.55	3.78	3.79	—	6.48	6.58	5.55	6.98br	6.98br	5.95	6.37	7.04
(5)	2.37	2.55	3.83	—	3.31	6.58	6.58	5.79	6.99	6.99	6.03	6.35	7.00
(11)[f]	2.38	2.53	3.84	3.84	—	6.52	6.58	6.08	6.89[b]	7.00[b]	6.89	—	6.42

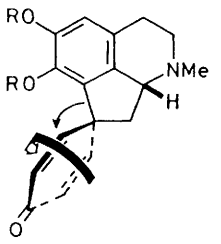
[a] Values of N-2' and N-6, C-2 and C-6', and 3-H and 5'-H are interchangeable. The chemical shift of the 1-OMe is δ 3.63 for (1), and 3.65 for (4). [b] d, J_o 8.5 Hz. [c] d, J_m 2.5 Hz. [d] d, J_o 9.7 Hz. [e] dd, J_o 9.7 Hz, J_m 2.5 Hz. [f] 9-H, δ 6.46 (d, J_o 9.7 Hz); 8-H (dd, J. 9.7 Hz, J_m 2.5 Hz); 12-H (d, J_m 2.5 Hz).

8-H (δ 6.15) experienced 11% and 13% signal enhancements, respectively. Similarly, irradiation of 12-H (δ 7.05) produced enhancements of 35% for 11-H (δ 6.35) and 8% for 6a-H (δ 3.41). On the other hand, irradiation of 8-H (δ 6.15) led to n.o.e's of 4% for the 10'-,11'-,13'-, and 14'-H broad singlet (δ 7.01), and 2% for the 1-OMe (δ 3.63), and 8% for 7α-H (δ 2.16). It follows that (+)-pakistanamine has the stereochemistry indicated in (1). Since the acetates of alkaloids (1)—(5) exhibit related c.d. curves,[1]‡ the alkaloids possess identical chirality. The n.m.r. spectral data for these alkaloids have been summarized in Table 1.

Immediately following the above findings, it was determined that the *B. valdiviana* extracts§ also supplied 1 mg of an amorphous alkaloid, (11), whose mass and u.v. spectra were essentially indistinguishable from those for valdiberine (3). The 360 MHz (Fourier transform) $CDCl_3$ n.m.r. spectrum, however, indicated a molecular arrangement significantly different from, and possibly isomeric with, valdiberine (Table 1). In particular, the absorption due to 10',11',13', and 14'-H, which is a broad singlet in valdiberine (3), appears as a well defined doublet of doublets in the new alkaloid, while the peaks due to 8'-H and the three vinylic protons of the dienone system are also substantially different in their chemical shifts from those for alkaloid (3).

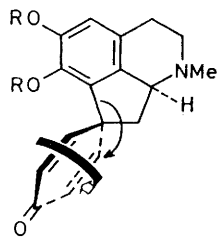
The c.d. curve of (11) is significantly different from that of valdiberine (3), a disparity which is reflected in the specific rotations for the two alkaloids, valdiberine being appreciably more dextrorotatory. At this stage, we could assume we had a new proaporphine-benzylisoquinoline, epivaldiberine (11), diastereomeric with valdiberine (3).

Since the amount of (+)-epivaldiberine available was insufficient for n.o.e. analysis, the whole sample was subjected to acid-catalysed dienone–phenol rearrangement. The sole product that could be isolated from this critical transformation proved to be the aporphine–benzylisoquinoline (−)-khyberine (12), whose absolute configuration is the same as



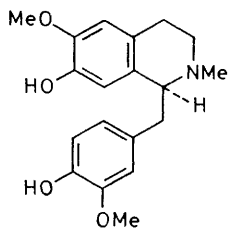
(14)

(*R*) configuration



(15)

(*S*) configuration



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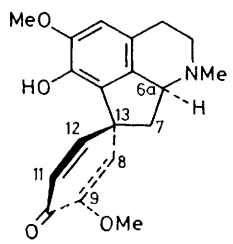

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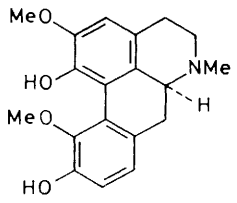

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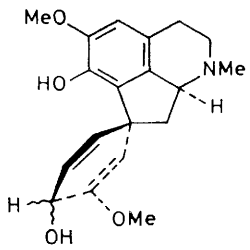

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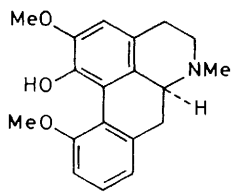

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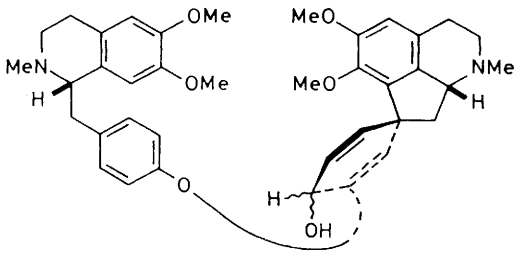

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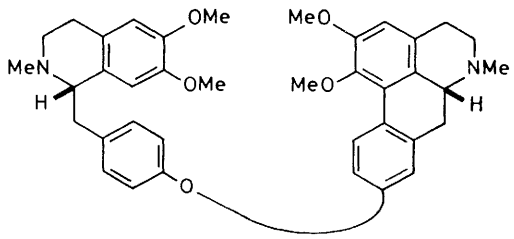

(22)

that of (+)-pakistanine (**7**), (−)-kalashine (**13**), and their *O*-methyl derivatives.[2] (+)-Epivaldiberine therefore has the 6a-(*R*) configuration, like all of the related aporphine- and proaporphine–benzylisoquinoline dimers isolated from *Berberis* species, and thus differs from (+)-valdiberine in the location of the substituent on the dienone. With both valdiberine and epivaldiberine the aryl ring migrates from C-13 to C-12 of the dienone ring which is *syn* to 6a-H, by means of a counter-clockwise rotation of ring D as indicated in expression (**14**).

Inspection of molecular models indicates that, in the starting proaporphine dimers (**1**)—(**5**), as well as in (**11**), it is the steric compression between the C-1 substituent and 8-H which induces this counter-clockwise motion, assisted by the proximity of, and hence the steric repulsion between, 12-H and 6a-H, and also between 8-H and 7α-H. Relief of steric compression is thus the sovereign factor governing the stereochemistry of the rearrangement of a proaporphine into an aporphine.

Attention was then turned to the known proaporphine alkaloid (−)-orientalinone (**17**), originally investigated in the 1960's, and whose stereochemistry at C-13 was not known.[3] (−)-Orientalinone is a derivative of (+)-orientaline (**16**), and its dienone–phenol rearrangement is known to yield (+)-1,10-dihydroxy-2,11-dimethoxyaporphine (**18**).[4] Since (−)-orientalinone (**17**) is epimeric with compounds (**1**)—(**5**) and (**11**) at C-6a, the aporphine product (**18**) can be rationalized as the result of aryl migration from C-13 to C-8, which again is *syn* to 6a-H, by means of a clockwise movement of the dienone system of orientalinone, as depicted in expression (**15**). (−)-Orientalinone is thus represented by (**17**). In this instance, it is the steric compression between the C-1 substituent and 12-H in species (**17**) which is important, together with the repulsion between 8-H and 6a-H, and also between 12-H and 7β-H.

A simple generalization that can be drawn is that proaporphines belonging to the C-6a-(*R*) configuration will undergo counter-clockwise rotation of the dienone system during the dienone–phenol rearrangement, as depicted in (**14**), while proaporphines of the (*S*) configuration will suffer a corresponding clockwise rotation as indicated in (**15**).

Relief of steric compression of the starting material also determines the stereochemical outcome of the closely related dienol–benzene rearrangement. It is known that reduction of (−)-orientalinone (**17**) affords a mixture of dienols (**19**) which undergo acid-catalysed rearrangement to the aporphine (+)-isothebaine (**20**).[3] As in the conversion of (**17**) into (**18**), a clockwise movement of ring D in species (**19**) takes place, to provide (**20**).

A related example of a dienol–benzene rearrangement concerns the known transformation of a mixture of pakistanaminols (**21**), obtained by reduction of (+)-pakistanamine (**1**),

into the aporphine–benzylisoquinoline (**22**) as the sole product.[1] A counter-clockwise rotation of ring D obtains in this case.

It is clear that in both instances of the dienol–benzene rearrangement discussed above, the stereochemistry of the leaving group has no bearing on the course of the reaction. Assuming a concerted mechanism, the rearrangement of a proaporphine dienol into an aporphine may be considered an example of an S_Ni' reaction in which the need to diminish the steric compression of the starting material is the cardinal fact governing the stereochemical aspects of the transformation.

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