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Reversal of Absolute Stereochemistry of the Pyrrolo[2,1-b]quinazoline Alkaloids Vasicine, Vasicinone, Vasicinol and Vasicinolone

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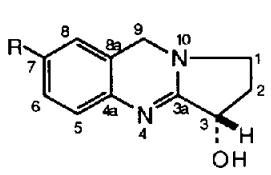
Abstract: The previously assigned 3*R* configuration of (-)-vasicinone has been reversed and this pyrrolo[2,1-b]quinazoline-9-one has been shown to have the 3*S*-configuration (**3**) on the basis of an X-ray diffraction study of (+)-vasicinone hydrobromide. Likewise, the 3*R* stereochemistry assigned earlier to (-)-vasicine (peganine) (**1**) on the basis of an X-ray analysis of its hydrochloride has also been reversed by reinvestigation of the X-ray diffraction analysis of the hydrobromide. The absolute stereochemistry of the alkaloids (+)-vasicinol (**2**) and vasicinolone (**5**) which have been interrelated, should also have the 3*S*-configuration. A study of the ^{1}H nmr spectroscopy of (-)-vasicine by the use of Mosher's method using MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters indicated an exception to this model for establishing the absolute configuration.

A number of plants belonging to the Acanthaceae, Cruciferae, Malvaceae and Rutaceae families have been shown to contain quinazoline alkaloids.[1] *Adhatoda vasica* Nees (Fam: Acanthaceae; Sanskrit: Vasaka) is an evergreen bush and extracts of the leaves are used in the Ayurvedic medicine as a remedy for cold, cough, bronchitis and asthma.[2] From the leaves, roots and the young plants, the pyrrolo[2,1-b]quinazoline alkaloids, (-)-vasicine (**1**) (peganine),[3-9] (+)-vasicinol (7-hydroxyvasicine) (**2**),[10] 5-methoxyvasicine,[8] (-)-vasicinone (**3**) and (±)-vasicinone (**4**),[5,7,9] 3-deoxyvasicinone,[9] vasicinolone (7-hydroxyvasicinone) (**5**),[7] adhavasinone (5-methoxyvasicinone),[11] vasicol,[12] vasicoline,[6] vasicolinone,[6] adhatodine,[6] anisotine,[6] and vasnetine,[13] have been reported. In view of the pharmacological activity of the pyrrolo[2,1-b]quinazoline alkaloids, it is important to establish the absolute configuration of some of these molecules.

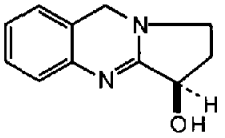
(-)-Vasicine, $C_{11}H_{12}N_2O$, mp 211-212°, $[\alpha]_D^{20}$ -254 is reported to be a respiratory stimulant, bronchodilator, uterine stimulant and an abortifacient.[1] The epimer, (+)-vasicine (peganine) (**6**) was isolated from *Peganum harmala* and has not been found in *A. vasica*. The absolute configuration of (-)-vasicine was determined as 3*R* based on the results of an anomalous dispersion X-diffraction study of (+)-vasicine hydrochloride, mp 205° (dec.), $[\alpha]_D^{20}$ + 30.8 which was derived from (-)-vasicine by treatment with HCl[14]. The conclusion was that (+)-vasicine·HCl has a 3*R* configuration, with the pyrrolidine ring in an envelope conformation and (-)-vasicine must also have a 3*R* configuration.

Since no crystal structure of any other pyrrolo[2,1-b]quinazoline alkaloids except 3-deoxyvasicine-zinc-complex[15] has been studied, we undertook to determine the absolute configuration of (-)-vasicinone, mp 201-202, $[\alpha]_D^{20}$ -122, isolated from the leaves of *A. vasica*.[13] The hydrobromide prepared by addition of MeOH-HBr to (-)-vasicinone, crystallized as colorless needles, mp 178-180°, $[\alpha]_D^{20}$ +15.1 (c=0.95, MeOH). X-Ray analysis of the hydrobromide[16] was carried out to establish the absolute configuration at C-3; the ORTEP drawing is shown in Figure 1.

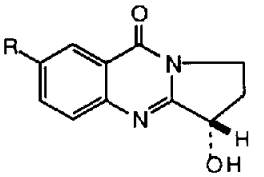
Intensity data were collected for both +h, +k, +l and -h, -k, -l indices for use in an anomalous dispersion analysis. For the enantiomer shown in Figure 1, the Flack parameter α[18] refined to a value of 0.035 (8) indicating a correct configuration. In addition, 44 out of 48 values of $| |F_c(h)| - |F_c(-h)| | > 1.0$ showed a correct trend for this enantiomer. The correct configuration for the HBr salt is therefore 3*S*. This was a surprising result because (-)-vasicine **1** on autoxidation or on oxidation with 30% H_2O_2 gives (-)-vasicinone.[5,13] We therefore determined an X-ray crystal structure of (-)-vasicine **1** and vasicine hydrobromide. The gross structure of (-)-vasicine-base was confirmed as (**1**).[19] The unit cell contains hydrogen-bonded dimers of vasicine related by an approximate non-crystallographic 2-fold axis relating the two independent molecules as in Figure 2.



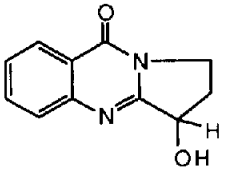
1 (-)-Vasicine R = H
2 (+)-Vasicinol R = OH



6 (+)-Vasicine



3 (-)-Vasicinone R = H
5 Vasicinolone R = OH



4 (±)-Vasicinone

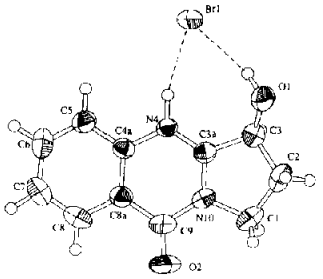
The crystal structure of (+)-vasicine·HBr, mp 193-195°, $[\alpha]_D^{20}$ + 27.5 (c 1.9, MeOH) prepared from (-)-vasicine, mp 213-214°, $[\alpha]_D^{20}$ -210 (C=2, $CHCl_3$) by addition of MeOH-HBr is isomorphous with the hydrochloride salt.[14,21] The four molecules per cell in space group $P2_1$ exist as molecular complexes with an approximate 2-fold axis relating the two independent molecules, as seen in Figure 3. The bromide ion makes close contact with both N4 and O1 in vasicine·HBr and vasicinone·HBr. The anomalous dispersion data strongly indicate that the correct configuration of (+)-vasicine·HBr is 3*S*.

Intensity data were collected for Friedel pairs of +h, +k, +l and -h, -k, -l for use in the anomalous dispersion study. The refinement of the Flack parameter for the enantiomer shown in Figure 3 gave a value of -0.025 (4), indicating that the correct configuration is 3*S* for (+) -vasicine·HBr. In addition, 103 out of 118 values of $| |F_c(h)| - |F_c(-h)| | > 1.0$ showed a correct trend for this enantiomer. Thus both anomalous dispersion studies show a consistent absolute configuration of 3*S* for both (-) - vasicine and (-)-vasicinone.

(+)-Vasicinol (7-Hydroxypeganine) (**2**) was isolated from the leaves of *A. vasica* [10] and Rajagopalan *et al.* reported its isolation from the roots of the same plant.[1,22] Bhatnagar *et al.* converted **2** to the monomethylether and showed it to be identical with authentic 7-methoxypeganine.[23] Vasicinolone (**5**) was isolated from the roots of *A. vasica* and also synthesized by oxidation of **2** with 30% H_2O_2. Szulzewsky *et al.* have stated that the absolute configurations of the naturally occurring alkaloids (-)-vasicinone (**3**) and (+)-7-hydroxypeganine (**2**) should be 3*R* on the basis of their X-ray structure analysis of (-)-vasicine·HCl.[14] The absolute configuration of **2**, and **5** should therefore be changed to 3*S*.

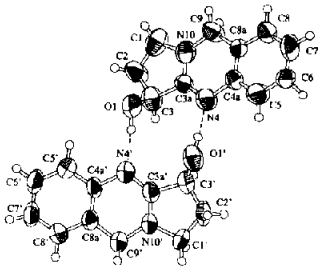
The anomalous dispersion study of Szulzewsky *et al.*[14] resulted in an erroneous configurational assignment because of one of the following reasons: (a) severe crystal decomposition during the data measurements likely caused large errors, (b) visually estimated film data of the chloride study could have large error limits, (c) chloride has smaller anomalous dispersion corrections than bromide and, thus, less observable differences in the Bijovet pairs and (d) only seven Bijovet pairs were compared in the chloride study. We also observed a problem of crystal decomposition of vasicine◊HBr when a crystal was exposed to air during the data collection. The problem of decomposition was ultimately avoided by mounting a crystal inside a sealed glass capillary.

On the basis of the new data, the absolute configurations of (-)-vasicine, (-)-vasicinone, (+) vasicinol and vasicinolone should be revised to 3*S*.



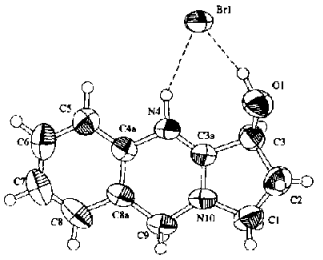
An ORTEP Plot of the Vasicinone-HBr Complex

Figure 1



An ORTEP PLot of the Vasicine H-Bonded Dimer

Figure 2



An ORTEP Plot of the Vasicine-HBr Complex

Figure 3

Absolute configurations of secondary alcohols have been determined by the use of Mosher's method.[24] This empirically derived correlation of configuration and ^{1}H nmr chemical shifts of the MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid] esters have been used in assigning absolute configurations of a number of naturally occurring compounds.[25] We prepared the *R*- and the *S*-MTPA esters of (-)-vasicinone (**3**). The ^{1}H chemical shift values $\Delta\delta = (\delta S - \delta R)$, for H-2$_\alpha$ (+ 12.5 Hz), H-2$_\beta$ (+ 45.0 Hz), H-1$_\alpha$ (+17.5 Hz), H-1$_\beta$ (+12.5 Hz) and H-3 (-12.5 Hz) suggested that (-)-vasicine should have the 3*R* configuration. As indicated by Mosher,[23] apart from the exception of borneol to conform to the empirical correlation, compounds having a heteroatom adjacent to the carbinyl proton profoundly change the molecular conformation on which the correlation is based. The fact that Mosher's method gives the opposite result, speaks to its own limitations. As Mosher's method of configurational assignment proved incorrect, we conclude that the absolute stereochemistry of these alkaloids is correctly determined by x-ray analysis.

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16. X-ray crystal data of (+)-vasicinone·HBr: $C_{11}H_{11}N_2O_2Br$, M_r = 283.12, orthorhombic, space group $P2_12_12_1$ (#19), a = 6.8406(4)Å, b = 10.4193(6)Å, c = 15.9478(9)Å, V = 1136.67(10)Å^3, Z = 4, D_C = 1.654g/cm^{-3}. Of the 2751 reflections measured on an Enraf-Nonius CAD4 diffractometer using Cu$K\bar{\alpha}$ radiation, 1394 were unique (R_{int} = 0.031), and 2274 had I>3σ(I) and were used for all calculations. The structure was solved by and expanded using Fourier techniques.[17] The non-hydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined and gave final R = 0.033; R_w = 0.039.
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19. X-Ray data of (-)-vasicine: $C_{11}H_{12}N_2O$, M_r = 188.23, orthorhombic, space group $P2_12_12_1$ (#19), a = 10.415(3)Å, b = 13.1523(4)Å, c = 14.0531(9)Å, V = 1925.1(3)Å^3, Z = 8, D_C = 1.299g/cm^{-3}. Of the 2234 reflections measured using Enraf Nonius CAD4 diffractometer using Cu$K\bar{\alpha}$ radiation, 1363 had I>3σ(I) and were used for all calculations. The structure was solved by direct methods[20] and expanded by Fourier techniques.[17] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were included but not refined and gave final R = 0.076; R_w = 0.092.
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21. X-Ray crystal data of (+)-vasicine·HBr: $C_{11}H_{13}N_2OBr$, M_r= 269.14, monoclinic, space group $P2_1$ (#4), a = 7.160(1)Å, b = 15.5934(7)Å, c = 10.2085(7)Å, V = 1138.1(2)Å^3, Z = 4, D_C = 1.571g/cm^{-3}. Of the 5163 reflections measured using Enraf Nonius CAD4 diffractometer using Cu$K\bar{\alpha}$ radiation, 2432 were unique (R_{int} = 0.036) and 4082 had I>3σ(I) and were used for all calculations. The structure was solved by direct methods[20] and expanded by Fourier techniques.[17] The non-hydrogen atoms were refined anisotropically and hydrogen atoms were included but not refined and gave final R = 0.043; R_w = 0.057.
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