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# A NEW GROUP OF ISOQUINOLINE ALKALOIDS

## THE SECOBERBINES

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**Abstract**—The new isoquinoline alkaloid (−)-peshawarine (**1**) has been isolated from *Hypecoum parviflorum* Kar. & Kir. (Papaveraceae). Its synthesis in the racemic form from coptisine (**6b**) involves a novel approach to cyclic hemiacetals in which the key step is the transformation of the aldehyde (±)-aobamine (**10b**) into the hemiacetal **12b** using ethyl chloroformate. (±)-Corydalisol (**11b**) and (±)-canadaline (**10a**) have also been synthesized for the first time. The absolute configuration of (−)-**1** was determined by chemical correlation with (+)-rhoeagenine methiodide (**20**). The chirality of the alkaloid (+)-canadaline (**10a**) has also been established by analogy to (+)-corydalisol (**11b**). (−)-Peshawarine (**1**), (+)-canadaline (**10a**), (+)-corydalisol (**11b**), and aobamine (**10b**), as well as hypecorine (**22**) and hypecorinine (**23**), are members of a new group of isoquinoline alkaloids, the secoberbines.

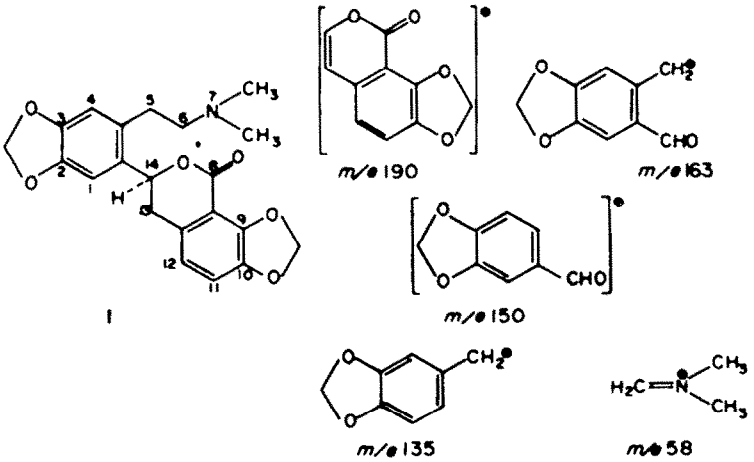
An investigation of the alkaloidal extracts from the shrub *Hypecoum parviflorum* Kar. & Kir. (Papaveraceae), native to northern Pakistan, resulted in our isolation of a new, colorless, non-phenolic, crystalline alkaloid (−)-peshawarine (**1**), $C_{21}H_{21}NO_6$, together with the known base protopine.[1] The IR spectrum of peshawarine shows a band at 1725 $cm^{-1}$ suggestive of a conjugated $\delta$-lactone.[2] The mass spectrum of the alkaloid possesses a very strong base peak at *m/e* 58, while other intense peaks are at *m/e* 383 ($M^+$), 190, 163, 150, 135 and 134 (= 135–H).

The PMR spectrum of the alkaloid in $CDCl_3$ reveals a six proton N-Me singlet at $\delta$ 2.26, a complex six proton H-5, H-6 and H-13 methylene proton absorption between $\delta$ 2.43 and 3.25, a one proton doublet of doublets at $\delta$ 5.55 and 5.73 (J = 4.5 Hz) due to H-14, a two proton methylenedioxy singlet at $\delta$ 5.98 assignable to the C-2,3 substituent, and another two proton methylenedioxy doublet of doublets at $\delta$ 6.11 and 6.18 (J = 1 Hz) attributable to the C-9,10 substituent. Four aromatic protons can be readily counted downfield, namely H-4 and H-1 as singlets at $\delta$ 6.66 and 6.98, respectively, and H-11 and H-12 as a doublet of doublets at $\delta$ 6.93 and 6.65 (J = 8 Hz), respectively.

In order to settle the positions of the substituents in peshawarine, the alkaloid was hydrogenolyzed using Pd as catalyst. Work-up furnished the crystalline amino acid **2**, $C_{21}H_{23}NO_5$, which proved to be identical in all respects with material obtained by similar reduction of the known alkaloidal salt (−)-bicuculline methochloride (**3**).[3]

Peshawarinediol (**4**), $C_{21}H_{25}NO_6$, the crystalline lithium aluminum hydride reduction product of **1**, has a mass spectrum with peaks at *m/e* 387 ($M^+$), 222, 177, 165, 164, 163 (= 164–H), 148 (= 165–OH), 135 (= 163–CO), and 58 (base). In particular, the presence of species *m/e* 222 and 165, each of which possesses three O atoms, confirms the existence of a $\delta$-rather than a $\gamma$-lactone in peshawarine (**1**).

To further eliminate the possibility of the alternate

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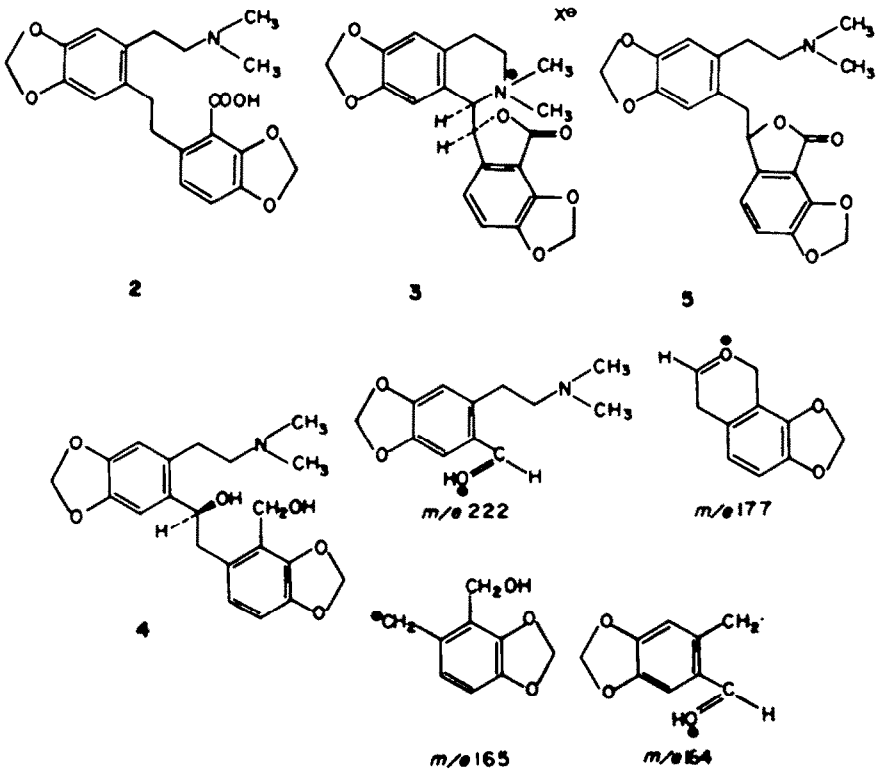
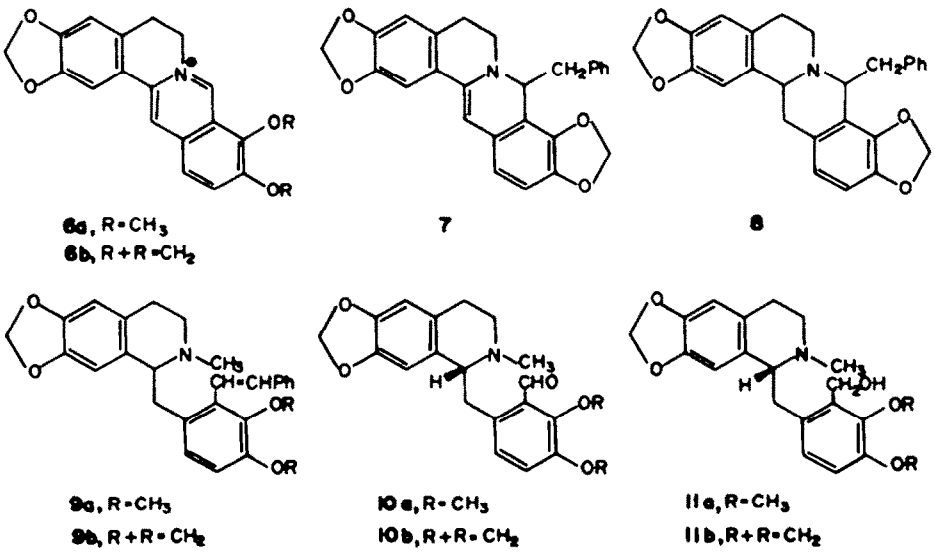


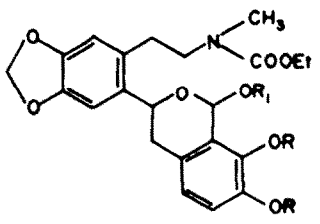

structure **5** for peshawarine which incorporates a γ-lactone, this molecule was synthesized from (−)-bicuculline methiodide (**3**) by a two step process involving a Hofmann elimination with cleavage of ring B, followed by hydrogenation of the stilbenoid double bond over Adams catalyst. The racemic γ-lactone **5** so obtained possesses a solution IR spectrum different from that of **1**, with a strong carbonyl absorption at 1772 $cm^{-1}$.

A synthetic effort was initiated at this stage. The peshawarine analog **16** was first synthesized from the known N-methyltetrahydrobenzylisoquinoline **9a** derived from readily available berberine (**6a**).[4,5] Lemieux–Johnson–Pappo oxidation of **9a** furnished the aldehyde **10a** in 89% yield. This aldehyde corresponds to the racemate of the naturally occurring base (+)-canadaline, recently found in *Hydrastis canadensis* L. (Ranunculaceae),[6] and the present preparation constitutes the first reported synthesis of this compound.

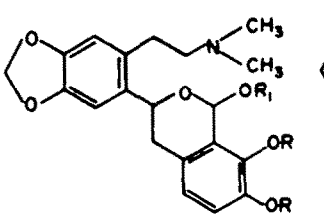
(±)-Canadaline (**10a**) was treated with ethyl chloroformate and aqueous potassium hydroxide to give hemiacetal **12a** as a colorless amorphous solid which tlc showed to consist of one pure compound. This procedure represents a new method for the preparation of cyclic hemiacetals, which in all likelihood proceeds by a two step process. Initially, the tertiary nitrogen is acylated to form a transient quaternary urethan. Subsequent attack by hydroxide at the aldehydic carbon with concomitant $S_N2$ displacement of the activated nitrogen gives rise to the product obtained.

The production of **12a** virtually guaranteed the success

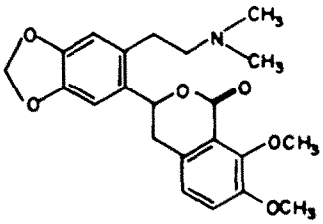




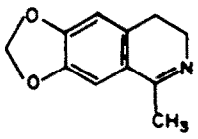
**12a**: $R_1 = H$, $R = CH_3$
**12b**: $R_1 = H$, $R + R = CH_2$
**13a**: $R_1 = R = CH_3$
**13b**: $R_1 = CH_3$, $R + R = CH_2$



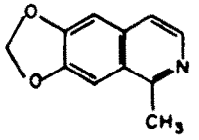
**14a**: $R_1 = CH_3$, $R = CH_3$
**14b**: $R_1 = CH_3$, $R + R = CH_2$
**15a**: $R_1 = H$, $R = CH_3$
**15b**: $R_1 = H$, $R + R = CH_2$



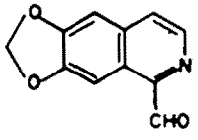
**16**



**17**



**18**



**19**

of the synthesis of the peshawarine analog **16** since all that remained to be achieved was the reduction of the N-carboethoxy group to an N-Me, and the oxidation of the cyclic hemiacetal to a $\delta$-lactone. To accomplish these changes, hemiacetal **12a** was first converted to its methyl acetal **13a** using trimethyl orthoformate. Lithium aluminum hydride reaction of **13a** in refluxing THF furnished the basic acetal **14a** in 78% yield. Finally, acid hydrolysis of **14a** followed by Jones oxidation gave rise to the required analog **16** of peshawarine. The yield of **16** from the basic acetal **14a** was 79% of theory.

The peshawarine analog **16** exhibits a CO absorption in the IR at 1725 $cm^{-1}$, and undergoes the same mass spectral fragmentations as natural (−)-peshawarine (**1**). Particularly diagnostic in the PMR spectrum of the analog is a doublet of doublets at $\delta$ 5.44 characteristically due to H-14.

Since a satisfactory method had now been developed for the preparation of compounds possessing the peshawarine skeleton from the corresponding protoberberine salt, it was deemed possible to synthesize (±)-peshawarine (**1**) by a parallel sequence if the protoberberine salt coptisine (**6b**) could be obtained in sufficient quantities. Since coptisine is not available from any commercial source, the production of this alkaloid by total synthesis was initiated.

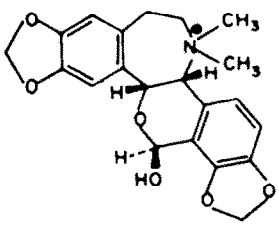
Of the sundry methods available in the literature for the preparation of 2,3,9,10-tetrasubstituted protoberberine salts, the sequence that appeared to be the most practical for a synthesis of coptisine (**6b**) was one proceeding through the intermediacy of an isoquinoline-1-carboxaldehyde as described by Bradsher.[7,8] In the course of the synthesis, however, it was found necessary to introduce some variations in the procedures for the preparation of the required isoquinoline **18** and the aldehyde **19**. The known dihydroisoquinoline **17**[9] was dehydrogenated with palladium in dry xylene at reflux to provide a 94% yield of the isoquinoline **18**. This result stands in contrast to the literature procedure where no solvent is used, and a much lower yield is obtained.[7] The next step involved the selenium dioxide oxidation of **18** to the isoquinoline-1-carboxaldehydr **19**. Satisfactory conditions for achieving this transformation have presently been determined to involve the use of *freshly prepared* selenium dioxide in *anhydrous* dioxane at reflux. Under these circumstances, the desired aldehyde **19** was obtained in 53% yield with an additional 24% recovery of starting material.

Following the sequence developed for the synthesis of the peshawarine analog **16**,[1] coptisine iodide (**6b**) was benzylated with benzylmagnesium chloride to afford a 92% yield of 8-benzyldihydrocoptisine (**7**) which was immediately reduced with sodium borohydride to 8-benzyltetrahydrocoptisine (**8**) in 95% yield. Quaternization with neat methyl iodide and Hofmann degradation afforded in high yield the oily benzylisoquinoline **9b**. When **9b** was oxidatively cleaved by means of osmium tetroxide and sodium metaperiodate, the expected aldehyde **10b** was obtained in 87% yield. Aldehyde **10b** corresponds to the racemic form of the alkaloid aobamine,[10] so that the present work represents the first reported synthesis of this compound recently found in *Corydalis ochotensis* Turcz. (Fumariaceae). Reduction of synthetic **10b** with sodium borohydride led to (±)-corydalisol (**11b**)[11,12] in essentially quantitative yield. Again, this alkaloid from *Corydalis incisa* (Thunb.) Pers. (Fumariaceae) had never previously been synthesized, and the present preparation constitutes the first reported total synthesis.

When (±)-aobamine (**10b**) was treated with ethyl chloroformate and aqueous potassium hydroxide, cyclization to the desired hemiacetal **12a** took place. Optimum yields were obtained by cooling the reaction mixture to 0° prior to addition of the ethyl chloroformate and base.

Successful conditions for the acetalization of **12b** were the mildest possible—dissolution of the hemiacetal in anhydrous methanol containing a trace of hydrogen chloride, and work-up after about 1 hr. The acetal **13b** could thus be produced in an overall yield of 77% from (±)-aobamine (**10b**). Lithium aluminum hydride reduction of **13b** supplied the basic acetal **14b** (80%), and hydrolysis of the latter was carried out by warming in 1:1 dioxane–5% hydrochloric acid. Finally, pyridinium chlorochromate in methylene chloride was found to be a superior reagent for the oxidation of **15b** to (±)-peshawarine (**1**), the yield being 82%.

Turning now to the problem of the absolute configuration of (−)-peshawarine (**1**), during the course of the present study it was noted that the dextrorotatory diol obtained through Emde degradation of (+)-rhoeagenine methiodide (**20**)[13,14] of known absolute configuration is



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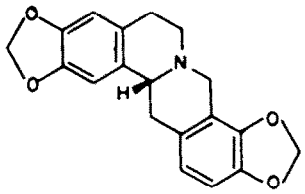

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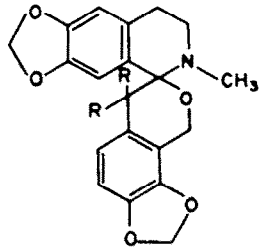
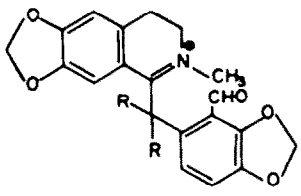


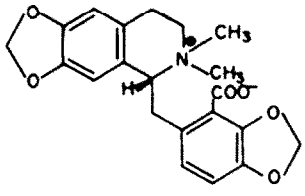
22, R=H

23, R+R=O



24, R=H

25, R+R=O



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identical with (+)-peshawarinediol (4) in terms of m.p., spectral characteristics and most significantly CD curve in methanol which shows $[\theta]_{293}$ + 10830° (pk), $[\theta]_{270}$ 0°, $[\theta]_{265}$ − 3483° (tr), $[\theta]_{252}$ 0°, and $[\theta]_{238}$ + 20124° (pk). The absolute configuration of naturally occurring (−)-peshawarine (1) is therefore rigorously established to be as indicated.[13]

The absolute configuration of (+)-corydalisol (11b) had previously been established by chemical correlation with (+)-stylopine (21) of known chirality.[11] Although the optical rotation was available for (+)-canadaline (10a), no stereochemical assignment had been made. Reduction of (+)-canadaline (10a) is reported to yield the corresponding alcohol canadalisol (11a), which is also dextrorotatory.[6] By analogy to (+)-corydalisol (11b), canadalisol and consequently (+)-canadaline (10a), must possess the identical absolute configuration.

It is now possible to define a new group of isoquinoline alkaloids, the secoberbines, which includes (−)-peshawarine (1), aobamine (10b), (+)-corydalisol (11b), and (+)-canadaline (10a), together with the racemic bases hypecorine (22)[16] and hypecorinine (23).[11,12,16] Due to the newness of the secoberbines, no biogenetic studies concerning their origin have been carried out; nevertheless several pathways can be conceived. Obvious starting materials are protoberberines or other oxidized and related alkaloids bearing the "berberine bridge" carbon appended to the lower ring. One can envision a precursory secoberbine such as 24 which could arise by oxidative cleavage of the N-7 to C-8 bond of a protoberberine. Enzymic reduction of the immonium bond would then furnish aobamine (10b); alternatively, reduction of the aldehyde followed by cyclization would yield hypercorine (22). Since 3,4-dihydrobenzylisoquinolines rapidly oxidize to the corresponding α-keto compounds,[17] 24 would be expected to oxidize to the iminoketone 25 which would cyclize to hypecorine (23). Oxidation-reduction of 24 succeeded by N-methylation could lead to production of the quaternary ammonium salt of a secoberbine carboxylic acid such as 26 which could then internally neutralize its charge by undergoing intramolecular $S_N2$ displacement of the quaternary nitrogen by the carboxylate anion to provide (−)-peshawarine (1) in a single step. The utilization of such a scheme, which incidentally is related to the one followed in the present work to obtain (±)-peshawarine, would furthermore account for the absolute configuration of (−)-peshawarine (1) being the reverse of that which obtains for the simple secoberbines (+)-corydalisol (11b) and (+)-canadaline (10a).

## EXPERIMENTAL

*Standard experimental conditions.* IR spectra were taken in $CHCl_3$ soln, and PMR spectra in $CDCl_3$ with TMS as internal standard. Mass spectra were obtained at 70 eV. All tlc was on Merck 254 silica gel plates. Microanalyses were by Midwest Microlab, Indianapolis, Indiana.

*Extraction.* The finely ground stems and leaves of *H. parviflorum* (3.8 kg) were extracted with petroleum ether, and the extracts discarded. The residual plant material was then extracted with EtOH. Evaporation of the solvent left a black tar which was stirred with 10% HCl. The acid soln was extracted with petroleum ether, and the non-basic extracts discarded. The acid soln was extracted with $CHCl_3$, and the $CHCl_3$ soln back extracted with 10% HCl. The $CHCl_3$ layer was evaporated to a thick tar, and triturated with petroleum ether; the petroleum ether was then discarded. The tar was dissolved in a small amount of $CHCl_3$, added to 100 g of silica gel, and evaporated to dryness. The powder was loaded onto a short, large diameter silica gel column packed in benzene, and eluted with benzene until the chlorophylls ceased to come off. The remaining adsorbed material was washed from the column with pure MeOH, and the solvent evaporated to yield Fraction A (4 g).

The HCl soln was basified to pH 8 with conc. $NH_4OH$, and extracted with $CHCl_3$. Evaporation of the solvent supplied Fraction B (10.2 g).

*(−)-Peshawarine* (1) was obtained from Fraction A by tlc on silica gel using $CHCl_3$ and MeOH (3:1). Recrystallization gave 1 (25 mg), m.p. 190–191° (MeOH); $[\alpha]_D^{25}$ − 109° (*c*, 0.2 MeOH); cd (*c*, 0.25 MeOH) $[\theta]_{290}$ + 15,950° (pk), $[\theta]_{277}$ 0°, $[\theta]_{260}$ − 17,400° (tr); $\lambda_{max}^{EtOH}$ 228, 245, 293 and 333 nm (log ε 4.96, 4.32, 3.78 and 3.69), $\lambda_{min}^{EtOH}$ 268 and 309 nm (log ε 3.46 and 3.55). High res. MS $M^+$ Calc. for $C_{21}H_{21}NO_6$: *m/e* 383.1368. Found: *m/e* 383.1394.

*Conversion of (−)-bicuculline methochloride (3) to amino acid 2.* The methochloride 3 (22 mg) in EtOH (500 ml) was hydrogenolyzed over 5% Pd/C (1 g) at 1800 psi and 78° for 24 hr. Purification by tlc yielded 2 (10 mg), m.p. 238–240° (MeOH); $\nu_{max}^{CHCl_3}$ 1600 $cm^{-1}$; $\lambda_{max}^{EtOH}$ 234 and 291 nm (log ε 2.17 and 2.01, PMR δ 2.83 (6H, s, $N(CH_3)_2$), 5.86 and 5.93 (4H, 2s, 2 $OCH_2O$),