

PESHAWARINE, AN UNUSUAL ISOQUINOLINE ALKALOID<sup>1,2</sup>

Maurice Shamma,\* Alan S. Rothenberg, and Gamini S. Jayatilake,

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

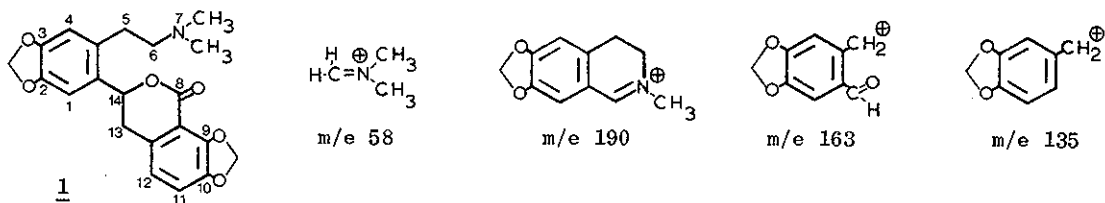
and S. Fazal Hussain

P.C.S.I.R. Laboratories, Peshawar, Pakistan

The alkaloid peshawarine (1), found in Hypocoum parviflorum, is a member of the new isoquinolinobenzopyran group of isoquinoline alkaloids. The analog 11 was synthesized from ( $\pm$ )-canadaline (6) derived from berberine.

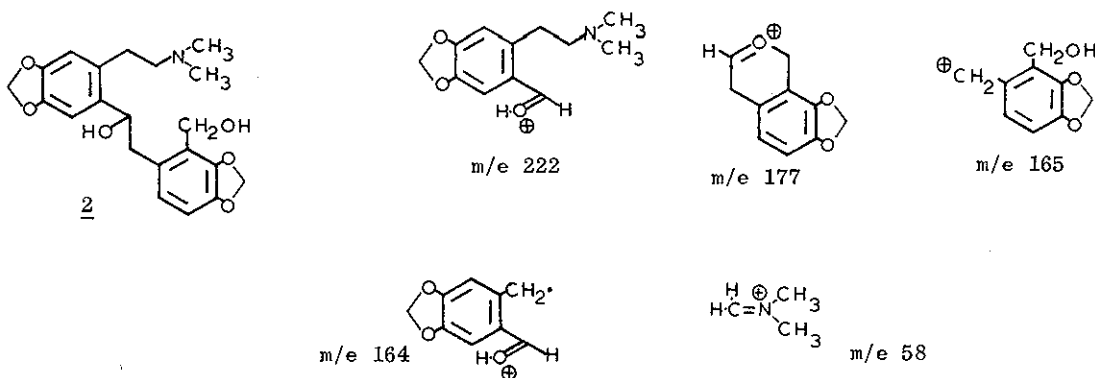
An investigation of the alkaloidal extracts from 3.8 kg of Hypocoum parviflorum Kar. & Kir. (Papaveraceae), collected in the vicinity of Peshawar, Pakistan, has yielded 25 mg of the colorless base peshawarine (1), C<sub>21</sub>H<sub>21</sub>NO<sub>6</sub>, mp 190-191<sup>0</sup> (methanol), [ $\alpha$ ]<sub>D</sub><sup>25</sup> -109<sup>0</sup> (c 0.2 methanol),  $\lambda_{\text{max}}^{\text{EtOH}}$  228, 245, 293 and 333 nm (log  $\epsilon$  4.96, 4.32, 3.78 and 3.69). The ir spectrum in chloroform shows no NH or OH absorption, but a strong peak at 1725 cm<sup>-1</sup> suggests the presence of a conjugated  $\delta$ -lactone.<sup>3</sup>

The mass spectrum of the alkaloid possesses a very strong base peak m/e 58, while other intense peaks are m/e 190, 163 and 135.



The  $\text{CDCl}_3$  (60 MHz) pmr spectrum of 1 exhibits an N-methyl singlet at  $\delta$ 2.26 (6H), a complex C-5, C-6 and C-13 methylene proton absorption between  $\delta$ 2.43 and 3.25 (6H), a doublet of doublets at  $\delta$ 5.55 and 5.73 ( $J = 4.5$  Hz) (1H) due to the C-14 proton, a methylenedioxy singlet at  $\delta$ 5.98 (2H) assignable to the substituent at C-2,3; and another methylenedioxy absorption, this time as a doublet of doublets, at  $\delta$ 6.11 and 6.18 ( $J = 1$  Hz) (2H) which can be attributed to the C-9,10 substituent. Finally, four aromatic protons can be counted downfield, namely the C-4 proton singlet at  $\delta$ 6.66, the C-1 singlet at  $\delta$ 6.98, and the C-11 and C-12 proton doublet of doublets at  $\delta$ 6.93 and 6.65 ( $J = 8$  Hz) (2H), respectively.

$\text{LiAlH}_4$  in ether reduction of peshawarine (1) affords the diol 2,  $\text{C}_{21}\text{H}_{25}\text{NO}_6$ , mp 133-136° (methanol),  $\lambda_{\text{max}}^{\text{EtOH}}$  225 and 288 nm ( $\log \epsilon$  4.21 and 3.63), whose mass spectrum shows, besides the molecular ion peak  $m/e$  387, strong peaks  $m/e$  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 oxygen atoms, confirms the existence of a  $\delta$ - rather than a  $\gamma$ -lactone in peshawarine.



In order to settle the positions of the substituents in peshawarine with certainty, the alkaloid was hydrogenolyzed in the presence of hydrogen and 5% Pd/C in ethanol at 1800 psi and 78° for 24 hrs. Work-up gave the amino acid 3,  $\text{C}_{21}\text{H}_{23}\text{NO}_6$ , mp 238-240° (methanol),  $\lambda_{\text{max}}^{\text{EtOH}}$  234sh and 291 nm ( $\log \epsilon$  3.38 and 3.22), mass spectrum  $m/e$  385 ( $\text{M}^+$ ),

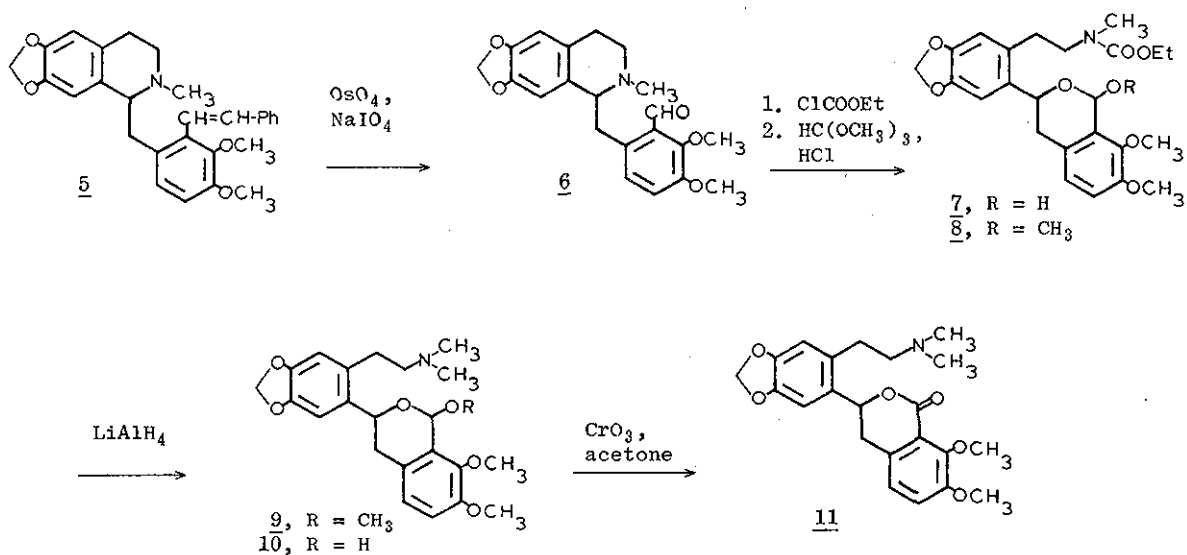
383, 340, 328, 179 and 58 (base), identical in all respects with material obtained by similar hydrogenolysis of the known (-)-biccuculline methochloride (4).<sup>4</sup>



To further confirm the structural assignment for peshawarine (1), a synthesis of the 9,10-dimethoxy analog 11 was carried out. The N-methyltetrahydrobenzylisoquinoline 5 derived from berberine<sup>5,6</sup> was cleaved with osmium tetroxide and sodium metaperiodate to the aldehyde 6, C<sub>21</sub>H<sub>23</sub>NO<sub>5</sub>, mp 139-140° (methanol),  $\nu_{\text{max}}^{\text{CHCl}_3}$  1685 cm<sup>-1</sup>. The preparation of 6 represents the first reported synthesis of the racemate of the alkaloid (+)-canadaline recently obtained from *Hydrastis canadensis* L.<sup>7</sup>

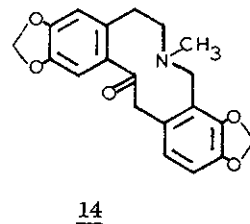
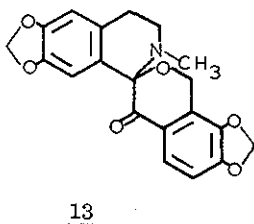
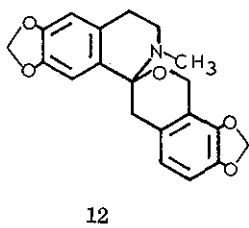
Reaction of ( $\pm$ )-canadaline (6) with ethyl chloroformate and potassium hydroxide in a CHCl<sub>3</sub>-ether-water biphasic system gave rise to the hemiacetal 7 which was immediately O-methylated with trimethyl orthoformate to the acetal urethan 8, mp 115-116° (methanol), C<sub>25</sub>H<sub>31</sub>NO<sub>8</sub>. LiAlH<sub>4</sub> in THF reduction of 8 yielded the new acetal 9, C<sub>23</sub>H<sub>29</sub>NO<sub>6</sub>, mp 104-105° (petroleum ether). Jones oxidation of the corresponding hemiacetal 10 then afforded the amorphous racemic peshawarine analog 11, C<sub>22</sub>H<sub>25</sub>NO<sub>6</sub>. Compound 11 exhibits  $\nu_{\text{max}}^{\text{CHCl}_3}$  1725 cm<sup>-1</sup>;  $\lambda_{\text{max}}^{\text{EtOH}}$  230, 247, 292 and 317 nm (log  $\epsilon$  4.38, 4.04, 3.60 and 3.31); nmr N-methyl singlet  $\delta$ 2.23 (6H), superimposed multiplet C-5, C-6 and C-13 methylene protons  $\delta$ 2.45-3.20 (6H), C-10 methoxyl singlet  $\delta$ 3.80 (3H), C-9 methoxyl singlet  $\delta$ 3.90, C-14 proton doublet of doublets  $\delta$ 5.33 and 5.55 (J = 4 Hz) (1H), C-2,3 methylenedioxy singlet  $\delta$ 5.78 (2H), C-4 proton singlet  $\delta$ 6.53 (1H), C-1 proton singlet  $\delta$ 6.88 (1H), and C-12 and C-11 protons as a doublet of doublets  $\delta$ 6.75 and 6.95 (J = 8 Hz) (2H), respectively.

The close similarity in the spectra of peshawarine (1) and 11 makes it clear that they are analogs belonging to the same series. The lowest yield in the individual steps leading from 5 to 11 was 75%.



Peshawarine is an unusual representative among what has so far been an unrecognized new group of isoquinoline alkaloids, namely the isoquinolinobenzopyrans. Recently characterized alkaloids which should be classified within this group are hyspecorine (12),<sup>8</sup> and hyspecorinine (13)<sup>8,9</sup> also known as corydalispirone.<sup>9</sup>

The biogenetic origin of the isoquinolinobenzopyrans is still unclear, but it seems likely that they are derived either from phthalideisoquinolines or from protopines. An accompanying alkaloid we have found in *H. parviflorum* is protopine (14) itself, and it is interesting to note that this ketonic base has been found in every *Hypocoum* species that has so far been investigated.<sup>8,10-12</sup>



References

1. This project was supported by NIH research grant CA-11450, awarded by the National Cancer Institute, PHS/DHEW. The authors are also grateful to Dr. S. Teitel of Hoffmann-La Roche, Inc., of Nutley, New Jersey, for a gift of bicuculline.
2. Elemental analyses were by combustion and/or high resolution mass spectrometry. The numbering system for peshawarine is by analogy with that for the protoberberines and the protopines.
3. R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds, 3rd ed., J. Wiley and Sons, Inc., New York (1974), p. 103.
4. R.H.F. Manske, Canad. J. Res., 1933, 8, 142.
5. M. Freund and K. Fleischer, Annalen, 1913, 397, 30.
6. J.R. Gear and I.D. Spenser, Canad. J. Chem., 1963, 41, 783.
7. J. Gleye, A. Ahond and E. Stanislas, Phytochemistry, 1974, 13, 675.
8. L.D. Yakhontova, M.N. Komarova, M.E. Perel'son, K.F. Blinova and O.N. Tolkachev, Khim. Prirod. Soedin., 1972, 624; Chem. Natural Compds., 1974, 592.
9. G. Nonaka and I. Nishioka, Chem. Pharm. Bull. (Japan), 1974, 23, 294.
10. T.F. Platonova, P.S. Massagetov, A.D. Kuzovkov and L.M. Utkin, Zh. Obshch. Khim., 1956, 26, 173.
11. S. Yu. Yunusov, S.T. Akramov and G.P. Sidiyakin, Dokl. Akad. Nauk UzSSR, 1957, 7, 23.
12. J. Slavík and I. Slavíková, Coll. Czech. Chem. Commun., 1961, 26, 1472.

Received, 4th May, 1976