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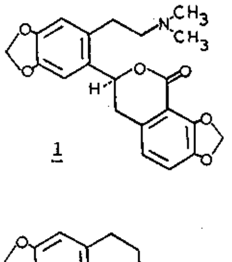
THE SYNTHESIS OF (±)-PESHAWARINE, (±)-AOBAMINE AND (±)-CORYDALISOL, AND THE ABSOLUTE CONFIGURATIONS OF (-)-PESHAWARINE AND (+)-CANADALINE[1,2]

Maurice Shamma and Alan S. Rothenberg,
Department of Chemistry, The Pennsylvania State University,
University Park, Pennsylvania 16802,
and S. Fazal Hussain,
P.C.S.I.R. Laboratories, Peshawar, Pakistan.

The first total syntheses of racemic peshawarine (1), aobamine (4) and corydalisol (5) have been achieved starting from synthetic coptisine (6). (-)-Peshawarine (1) has been interrelated with (+)-rhoeagenine methiodide (14) of known chirality. The absolute configuration of (+)-canadaline (16) has also been established through correlation with (+)-stylopine (18) of known stereochemistry.

The characterization of the alkaloid (-)-peshawarine (1) has previously been described, together with the synthesis of the racemic analog 2 derived from berberine (3).[3] We now wish to report the first total synthesis of (±)-peshawarine (1), and of the racemates of the related naturally occurring secoberbines aobamine (4)[4] and (+)-corydalisol (5)[5] starting from synthetic coptisine iodide (6).[6,7]



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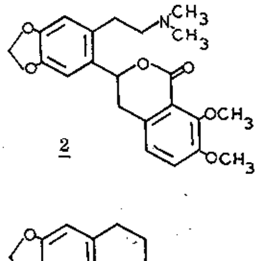

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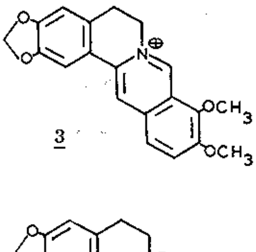

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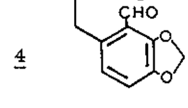

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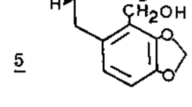

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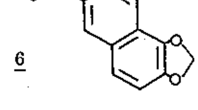

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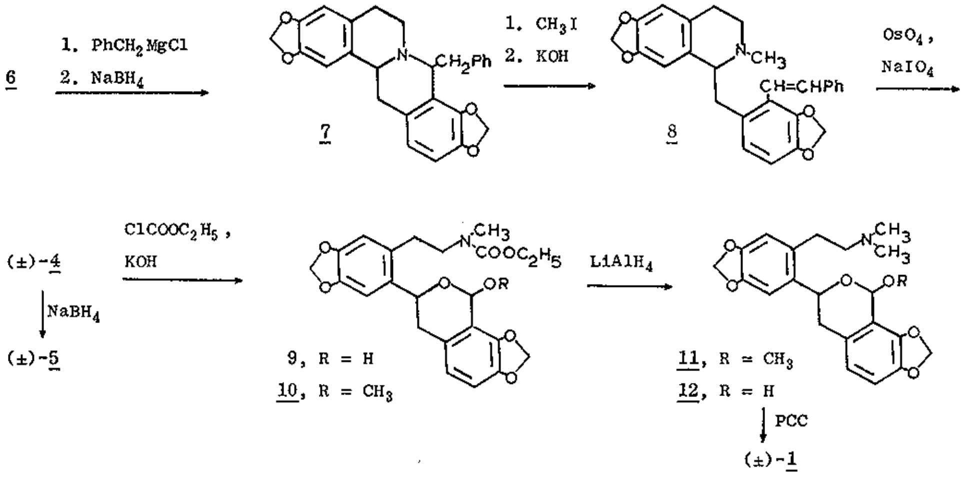
Coptisine iodide (6) was benzylated with benzylmagnesium chloride to furnish 8-benzyldihydrocoptisine which, without purification, was reduced with $NaBH_4$ in methanol to provide an 88% yield of 8-benzyltetrahydrocoptisine (7), $C_{26}H_{23}NO_4$, mp 162-164° (MeOH); methiodide salt, $C_{27}H_{26}NO_4I$, mp 207-209° (EtOH), Scheme I. Hofmann degradation of the methiodide salt using methanolic KOH afforded an 87% yield of the oily benzylisoquinoline 8, $C_{27}H_{25}NO_4$.

Lemieux-Johnson-Pappo oxidation of 8 gave rise to (±)-aobamine (4), $C_{20}H_{19}NO_5$, mp 168-168.5° (MeOH), $\nu_{max}^{CHCl_3}$ 1685 cm^{-1}, in 87% yield. Reduction of (±)-aobamine (4) with $NaBH_4$ led quantitatively to the previously unsynthesized (±)-corydalisol (5), $C_{20}H_{21}NO_5$, mp 127-128° (MeOH), $\nu_{max}^{CHCl_3}$ 3160 cm^{-1}.

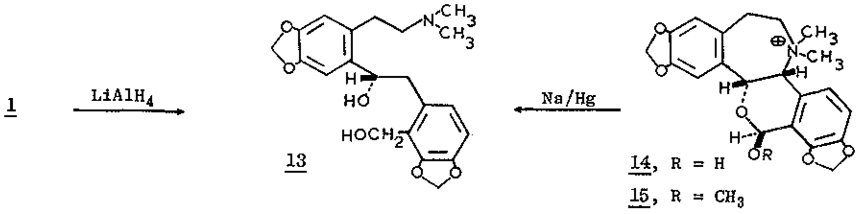
When (±)-aobamine (4) was treated with ethyl chloroformate and KOH, intramolecular displacement occurred leading in 77% yield to hemiacetal 9 which was rapidly and quantitatively converted to acetal 10, $C_{24}H_{27}NO_8$, mp 126-126.5° (MeOH), using methanol containing a trace of HCl.

The basic acetal 11, $C_{22}H_{25}NO_6$, mp 197-198° (ether), was generated in 80% yield upon $LiAlH_4$ in THF reduction of the urethan acetal 10. Acid hydrolysis of 11 provided hemiacetal 12 which was oxidized with pyridinium chlorochromate to the desired (±)-peshawarine (1), $C_{21}H_{21}NO_6$, mp 182-183° (MeOH), in 80% yield from 11 (Scheme I). Synthetic racemic 1 was identical with the levorotatory alkaloid in terms of tlc R_f values, and pmr and mass spectra.

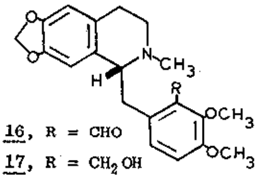
Scheme I

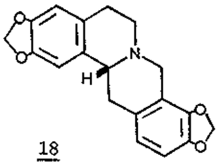


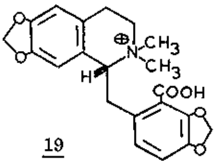
Turning now to the determination of the absolute configuration of (-)-peshawarine, (+)-peshawarinediol (13), obtained from $LiAlH_4$ reduction of the natural alkaloid,[3] is identical in terms of mp, spectral properties and circular dichroism curve with the Emde degradation product from (+)-rhoeagenine methiodide (14)[8,9] of known absolute configuration, so that the stereochemistry of (-)-peshawarine (1) and (+)-peshawarinediol (13) must be as indicated.[10]



Perusal of the literature also allowed the assignment of absolute configuration to the secoberbine alkaloid (+)-canadaline (16). (+)-Corydalisol (5) has been interrelated chemically with the tetrahydroprotoberberine (+)-stylopine (18) of established chirality.[5] Reduction of (+)-canadaline (16) is known to yield (+)-canadalisol (17).[11] By analogy to (+)-corydalisol (5), (+)-canadalisol (17), and consequently (+)-canadaline (16), must possess the identical absolute configuration. The optical rotation of aobamine (4) has not been reported. It is likely, however, that it too will be found to be dextrorotatory.


16, R = CHO
17, R = CH_2OH


18


19

Since the absolute configuration of (-)-peshawarine (1) differs from that of the other secoberbines discussed here, it can be adumbrated that in nature a secoberbine such as 19, derived from oxidative cleavage of a protoberberine, might undergo intramolecular S_N2 displacement at the asymmetric center to generate (-)-peshawarine (1).

References

1. This project was supported by NIH research grant CA-11450, awarded by the National Cancer Institute, PHS/DHEW.
2. Elemental analyses were by high resolution mass spectrometry and/or combustion analysis.
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4. T. Kametani, M. Takemura, M. Ihara and K. Fukumoto, Heterocycles, 4, 723 (1976).
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6. C.K. Bradsher and N.L. Dutta, J. Org. Chem., 26, 2231 (1961).
7. Coptisine iodide was obtained by us through mercuric acetate oxidation of (±)-stylopine (18) which was synthesized through the intermediacy of 6,7-methylenedioxyisoquinoline-1-carboxaldehyde. Substantial modifications of the literature method were introduced so as to make the sequence preparatively useful. These modifications will be discussed in a full paper.
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9. V. Šimánek, A. Klásek, L. Hruban, V. Preininger and F. Šantavý, Tetrahedron Lett., 2171 (1974).
10. It is known (Refs. 8 and 9 above) that Emde degradation of (+)-rhoeadine methiodide (15) leads to optically active acetal 11. It follows that (+)-15 should be convertible to (−)-peshawarine (1) by a three step sequence involving Emde reductive cleavage to the acetal 11, acid hydrolysis of 11 to the hemiacetal 12, and PCC oxidation. However, (+)-rhoeadine methiodide (15) was not available to us to allow for these transformations.
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