Tetrahedron Letters No.24, pp. 1513–1519, 1964. Pergamon Press Ltd.
Printed in Great Britain.

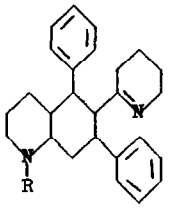
THE STRUCTURE OF LOBINALINE

Michael M. Robison, William G. Pierson, L. Dorfman,
B. F. Lambert and Robert A. Lucas

Research Department, CIBA Pharmaceutical Company,
Division of CIBA Corporation, Summit, New Jersey

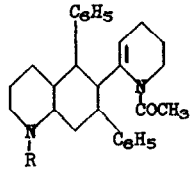
(Received 11 April 1964)

Lobinaline, the major alkaloid of Lobelia cardinalis L., was first isolated in 1938 by Manske (1), who carried out some preliminary chemical studies on the constitution of the compound. Since that time little has been published on the subject other than a report (2) on the paper chromatographic behavior of the alkaloid. In the course of a program of routine plant screening we isolated a crystalline alkaloid from Lobelia cardinalis, which appears to be the same as the earlier reported lobinaline. We wish to report here the results of degradative, spectral and synthetic studies which have enabled us to assign skeletal structure 1a to lobinaline (stereochemistry unspecified).



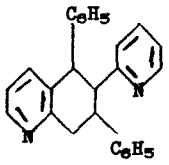
1 a, R = CH_3

b, R = H

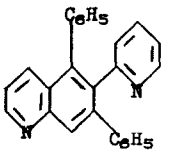


2 a, R = CH_3

b, R = CN



3



4

Manske reported lobinaline to be a crystalline substance, m.p. 94-95°, $[\alpha]_D^{24}$ +22.3°, with the empirical composition $C_{28}H_{36}N_2O$, though this formula was later recognized as that of a monohydrate and modified to $C_{28}H_{36}N_2$ (3). In this laboratory the alkaloid was isolated by what was essentially Manske's method, except that the crude free base was purified as such by chromatography on alumina. In this manner crystalline material was readily obtained. Although the melting points of various batches were somewhat variable, an analytical sample obtained by recrystallizations from hexane and sublimation had m.p. 108-110°, $[\alpha]_D^{26}$ +38° ($CHCl_3$). The analysis,[1] mass spectrum and n.m.r. spectrum[2] of the alkaloid as well as the structural studies indicated that the correct empirical formula is $C_{27}H_{34}N_2$. The ultraviolet spectrum showed only benzene absorption, while the infrared indicated the absence of NH groups and the presence of a monosubstituted benzene moiety. A strong absorption band was also observed at 1665 $cm.^{-1}$. Potentiometric titration showed the presence of two weakly basic groups with pK_A values of 5.7 and 8.2, while the mass spectrum showed a small

---

1. Satisfactory analytical values were obtained for all compounds reported.

2. Spectra were obtained with the Varian A-60 spectrometer at 60 mc./sec. using tetramethylsilane as the internal reference in deuteriochloroform solution. Chemical shifts are quoted in field-independent δ units (p.p.m.) and coupling constants are expressed in c.p.s.

parent peak at 386, the strongest signal at 186 (100%), and further significant peaks at 200 (90%), 201 (40%) and 187 (20%). The n.m.r. spectrum confirmed the proton count as well as the presence of two monosubstituted benzene rings and revealed the presence of one N-methyl group but no vinyl protons.

The alkaloid proved itself remarkably inert to a variety of reduction and dehydrogenation reagents. The degradation scheme finally employed followed from the initially somewhat unexpected observation that the substance reacted readily with refluxing acetic anhydride to form a monoacetyl derivative, $C_{29}H_{36}N_2O$. The appearance of a single broad vinyl proton signal in the n.m.r. spectrum of the derivative (indicative of a $\rangle C{=}CH\text{-}CH_2$ group) and of a split absorption band at 1670 and 1655 $cm.^{-1}$ in the infrared, together with the ready hydrolysis of the derivative to regenerate lobinaline, suggested acetylation of a 6-substituted 2,3,4,5-tetrahydropyridine (or a similar ring system) at the nitrogen atom, and eventually allowed formulation of the acetyl derivative as 2a. Acetyllobinaline, m.p. 159-160°, was further characterized by a single pK_A value of 8.2 and $[\alpha]_D^{26}$ +67° ($CHCl_3$).

Treatment of acetyllobinaline with cyanogen bromide in ether resulted almost exclusively in demethylation without ring opening to form the corresponding desmethyl N-cyano compound (2b), $C_{29}H_{33}N_3O$. Although this substance could not be obtained in crystalline form, the amorphous glass was brought to analytical purity by chromatography on alumina and evaporative distillation in vacuo. The nitrile amide, $[\alpha]_D^{24}$ +64°, showed strong infrared absorptions at 2215, 1670 and 1650 $cm.^{-1}$.

Hydrolysis and decarboxylation of 2b in refluxing 6N hydrochloric acid led to the formation of desmethyllobinaline (1b), $C_{28}H_{32}N_2$, again obtained only as an uncrystallizable glass, but again purified by chromatography and evaporative distillation. The observed optical rotation was, coincidentally, $0 \pm 2°$. The infrared spectrum was very similar to that of lobinaline, except for the appearance of a broad, weak NH band in the 3200-3300 $cm.^{-1}$ region.

Dehydrogenation of desmethyllobinaline was effected by palladium-charcoal in refluxing diphenyl ether. Difficulty was at first encountered in the separation of the reaction products, and repeated chromatography on alumina afforded only the partially dehydrogenated 3 ($C_{28}H_{22}N_2$) in crystalline form. It was apparent from the ultraviolet spectra that the substance, m.p. 121-122°, $[\alpha]_D^{27}$ +161°, contained two isolated alkylpyridine rings. In ethanol solution the values for $\lambda_{max.}$ mμ (ϵ) were 262 (7920), 269 (7830) and 277 (4520) and minima were observed at 235 (1870), 266 (7560) and 275 (4470). In acid solution the maximum was observed at 267 (13700) and the minimum at 236 (4130). Further, the n.m.r. spectrum revealed the presence of two overlapping α-pyridine protons centered at 8.47 p.p.m. as well as four aliphatic protons at 3.4-3.9 (complex) and one tertiary aliphatic proton centered at 4.88. The last-named appeared as a doublet (J = 10.4) with indication of additional long-range coupling. Treatment of the compound with sodium methoxide in deuteriomethanol at 100° for two weeks resulted in about 40% replacement of the 4.88 p.p.m. proton by deuterium[3] and about 80% replacement of two

3. It is interesting to note that although the intensity of the 4.88 p.p.m. band was reduced, the general shape was unchanged, indicating that the other protons involved in the long-range coupling were not greatly affected.

of the protons in the 3.4-3.9 region. In the latter signal it was now possible to recognize the presence of an AB quartet (J = 11.8) which became still more easily recognizable when the signal at 4.88 p.p.m. was decoupled[4].

Chemical evidence for the nature of the bonding of the pyridine rings was gained by oxidation of 3 with potassium permanganate. Although extensive degradation of the pyridine rings was encountered, it was possible to isolate (in addition to benzoic acid) a very small, polar, acidic fraction which had an ultraviolet absorption maximum at 262 mμ. Since the quantity obtained was insufficient for separation, the mixture was methylated directly with diazomethane and compared by paper and thin-layer chromatography with known methyl esters of pyridine mono- and dicarboxylic acids. Comparisons in several systems demonstrated that the two oxidation products obtained were dimethyl quinolinate and methyl picolinate. It could thus be concluded at this point that the pyridine ring yielding methyl picolinate represented the original tetrahydropyridine grouping in lobinaline (5) since a vinyl proton had been observed on acetylation; accordingly, the ring yielding dimethyl quinolinate represented an N-methylpiperidine moiety (6).

5

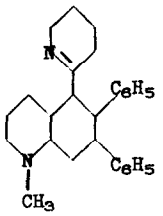
6

4. We wish to thank Professor E. Wenkert of the Department of Chemistry, Indiana University, for his kindness in carrying out the spin-spin decoupling experiments on a Varian HR-60 instrument.

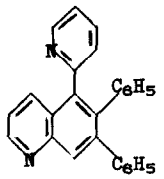
The preceding results became much clearer when an effective method for separating the total desmethyllobinaline dehydrogenation mixture was found and when, for the first time, the completely dehydrogenated 4, $C_{26}H_{18}N_2$, was obtained in crystalline form. The two dehydrogenation products were separated essentially completely by partitioning between methylene chloride and 0.1 N hydrochloric acid in seven funnels. The weaker base 4, m.p. 156-157° was optically inactive and showed only aromatic proton signals in the n.m.r. The isolation of an aromatic product which differed from 3 by the loss of four hydrogens prompted the recognition of a possible quinoline-tetrahydroquinoline relationship. The ultraviolet spectrum of 4 was entirely consistent with that of a quinoline bearing three large, planar, aromatic rings in adjacent positions, with resulting marked steric inhibition of conjugation. The maximum was observed at 242 mμ (41000) with a shoulder at 320 (4600) while the minimum was found at 226 (3280). These data, together with consideration of the frequent occurrence of the phenylethylpiperidine moiety in alkaloids of related Lobelia species, suggested 4 as the most likely structure for the quinoline and structure 1a for lobinaline itself. These structures were also compatible with the previously mentioned deuteration studies on 3, on the basis that the two replaceable protons at 3.4-3.9 p.p.m. would be C_8 hydrogens and the partially replaced 4.87 p.p.m. proton would be in the 5-position. If the α-picolyl proton at C_8 were prevented from exchanging by steric effects, then the two unexchanged 3.4-3.9 p.p.m. protons would occupy positions 6 and 7 of the ring and would be expected to appear as doublets, as observed, on blanking out of the C_5 and C_8 hydrogens by deuteration and decoupling.

Although the above data, together with biogenetic considerations,

seemed to point most strongly to structure la for lobinaline, it was felt that they were not sufficiently conclusive definitely to preclude the biogenetically less attractive expressions 7 for lobinaline, and 8 for the dehydrogenated compound. This question was settled conclusively by independent, unequivocal syntheses of the two isomeric diphenylpyridylquinolines. The synthesis of 4 resulted in a material which was identical in all respects with the natural degradation product as shown by infrared, ultraviolet and mixture melting point comparison. The synthesis of the isomeric 8 resulted, as expected, in a product with a similar ultraviolet spectrum, but with m.p. 193-194° and an infrared spectrum which differed greatly in positions of absorption bands in the fingerprint region. The details of these two independent syntheses will be reserved for a later full publication on lobinaline.



7



8

References

(1) R. H. F. Manske, Can. J. Research 16B, 445 (1938)

(2) F. Kaczmarek and E. Steinegger, Pharm. Acta Helv. 33, 852 (1958)

(3) Reference 2, footnote 2