COMMUNICATIONS

Particle-Size Distributions of Milled Granulations and Powders

To the Editor:

Steiner et al. (1) recently demonstrated that milling of monodisperse granulations gives rise to log-normally distributed particle sizes. Log-normal distributions are not uncommon for solid particles; crystallization often leads to log-normal distributions that are truncated from below and above, a fact that has been explained (2) on theoretical grounds. However, no explanation has been put forth on why milling produces a log-normal distribution. Such an explanation may be sought in the following simplfied theoretical model.

Let it be assumed that a sample of N particles of size x_0 is milled and that a fraction, α, of the particles is "halved" on each impact. It follows that there will be $(N)(1 - \alpha)$ particles left of the original size after one impact and $(N)(1 - \alpha)^2$ left after two impacts. After the second impact there will be $(N)(4)(\alpha)(1 - \alpha)$ of size $x_0/2$ and $(N)(4)(\alpha^2)$ of size $x_0/(2^2)$. The total number of particles after the second impact is $(N)(1 + \alpha)^2$. The number of particles of size x_0, $x_0/2$, $x_0/(2^2)$, and $x_0/(2^3)$ after zero, one, two, three, and m impacts is listed in Table I. It is

seen from the bottom line of the table that the total number of particles after m impacts is $(N)[(1 + \alpha)^m]$. After m impacts the possible particle sizes are $x_0/(2^p)$, where p is an integer between zero and m. The number of particles of size $x = x_0/(2^p)$ is seen from the last column of Table I to be:

$$N \begin{bmatrix} m \\ p \end{bmatrix} [(2\alpha)^p][(1 - \alpha)^{m-p}] \qquad \text{(Eq. 1)}$$

i.e., since the number of particles is $(N)[(1 + \alpha)^m]$, the fraction having a particle size of $x = x_0/(2^p)$ is given by:

$$Pr[(x_0/2^p)] = [(1 + \alpha)^{-m}]\begin{bmatrix} m \\ p \end{bmatrix}[(2\alpha)^p][(1 - \alpha)^{m-p}] \quad \text{(Eq. 2)}$$

The right-hand side of Eq. 2 is a normalized binomial expression which, for large values of m, approaches a normal distribution. The *sizes* of the particles, however, are log-linear; for instance, $\log(2^{p+1}) - \log(2^p) = \log 2$, regardless of the value of p. Hence, for large m, the distribution described by Eq. 2 approaches a log-normal equation.

The same type of argument holds for any situation where the particle breaks into a number of equally sized fractions. The model is, of course, greatly simplified since it assumes that an impact will always produce the same (whether two, three, or more) fractional particles, and it does not account for removal of fines. However, the model describes the main feature of milling which accounts for the log-normally distributed end-product.

(1) G. Steiner, M. Patel, and J. T. Carstensen, *J. Pharm. Sci.*, 63, 1395(1974).

(2) R. R. Irani and C. F. Callis, "Particle Size: Measurement,

Table I—Number of Particles Remaining after Number of Indicated Impacts[a]

| Size | Impacts | | | | |
	0	1	2	3	m
x_0	N	$(N)(1 - \alpha)$	$(N)[(1 - \alpha)^2]$	$(N)[(1 - \alpha)^3]$	$(N)[(1 - \alpha)^m]$
$x_0/2$		$(N)(2\alpha)$	$(N)(2)(2\alpha)(1 - \alpha)^b$	$(N)(2)(2\alpha)[(1 - \alpha)^2]$	$(N)\begin{bmatrix} m \\ 1 \end{bmatrix}(2\alpha)[(1 - \alpha)^{m-1}]$
$x_0/4$			$(N)(4)(\alpha^2)$	$(N)(3)[(2\alpha)^2](1 - \alpha)$	$(N)\begin{bmatrix} m \\ 2 \end{bmatrix}[(2\alpha)^2][(1 - \alpha)^{m-2}]$
$x_0/8$				$(N)[(2\alpha)^3]$	$(N)\begin{bmatrix} m \\ 3 \end{bmatrix}[(2\alpha)^3][(1 - \alpha)^{m-3}]$
Total	N	$(N)[(1 + \alpha)]$	$(N)[(1 + \alpha)^2]$	$(N)[(1 + \alpha)^3]$	$(N)[(1 + \alpha)^m]$

[a] Initial number is N. [b] The general procedure is to note that the amount of size $x_0/2$ disappearing is $N\alpha 2\alpha$; $N2\alpha(1 - \alpha)$ remains. The amount of $x_0/2$ produced from size x_0 is twice $N\alpha(1 - \alpha)$, so the amount of size $x_0/2$ produced is $(N)(2\alpha)(1 - \alpha)$. The total is $(2)(N)[\alpha(1 - \alpha)]$.

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# Alkaloids of *Lindera benzoin* (L.) Blume (Lauraceae) I: Isolation and Identification of Laurotetanine

To the Editor:

The isolation of aporphine alkaloids from other *Lindera* species (1, 2) and the reported cytotoxic activity of certain aporphines (3, 4) led to this investigation of the native *Lindera benzoin* (L.) Blume (Lauraceae), known commonly as spicebush.

L. benzoin plants were collected locally[1]. The stems were separated from the leaves and roots, air dried, and ground for extraction. Preliminary TLC examination indicated one major and at least five minor nonquaternary alkaloids.

The stem material (36.3 kg) was defatted with *n*-hexane[2], and this alkaloid-free extract was reserved for further study. The defatted material was macerated and exhaustively extracted with methanol by percolation. The viscous residue (1.6 kg) remaining after removal of the methanol *in vacuo* at 40° was stirred with 0.1 M citric acid, vacuum distilled to remove the remaining traces of methanol, and filtered. The acid solution was alkalinized with ammonium hydroxide solution and extracted with chloroform. A phenolic fraction (38.5 g) and a nonphenolic fraction (4.0 g) were prepared from the chloroform solution by the method of Johns and Lamberton (5).

The dark-brown phenolic fraction was extracted with benzene to yield an orange benzene-soluble residue (23.5 g) which was found to contain the major alkaloid (I) by TLC [silica gel G, chloroform–methanol (9:1)]. A total of 0.4 g of I was separated from 0.6 g of the benzene-soluble phenolic residue by preparative

I
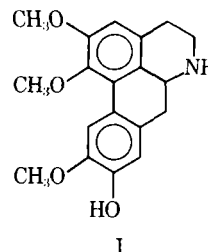
TLC [silica gel[3], chloroform–methanol (9:1)] and was further purified by precipitation from hot cyclohexane to yield a cream-colored amorphous precipitate (II) which failed to crystallize from the usual solvents. Compound II gave a single spot with several TLC solvent systems and $[\alpha]_D^{25}$ + 94.6° (c 0.38 in ethanol). The mass spectrum showed the apparent molecular ion at m/e 327 (72%) followed by other prominent peaks at m/e 326 (100%), 312 (23), 310 (10), and 296 (16). The UV absorption spectrum showed λ_{max} (C_2H_5OH) 219 (log ϵ 4.51), 282 (4.2), and 304 (4.19) nm; λ_{max} (C_2H_5OH–NaOH) 232 and 329 nm; and λ_{min} (C_2H_5OH–NaOH) 270 nm.

The NMR spectrum run in deuterated chloroform, with tetramethylsilane as the internal standard, showed one aromatic proton at $\delta 8.08$, 6.61, and 6.08, three methoxyl protons at $\delta 3.70$, six methoxyl protons at $\delta 3.91$, and no N-methyl protons as shown by the absence of a signal at the $\delta 2.5$ region. The specific rotation (6), mass spectroscopy (7, 8), UV (9), and NMR (10) data suggested that II could be identified as the noraporphine alkaloid laurotetanine. The identification of II as laurotetanine was confirmed by co-TLC and by comparison of the IR, UV, and mass spectroscopy data with those derived from authentic laurotetanine. Furthermore, preparation of the N-methyl hydrobromide derivative of II furnished a crystalline product that gave melting points and IR, UV, and mass spectroscopy data in good agreement with those derived from authentic N-methyllaurotetanine hydrobromide.

This is the first report in the literature of the occurrence of laurotetanine in *L. benzoin*. The isolation and identification of other alkaloids from *L. benzoin* will be reported later.

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[1] The plants were collected in September 1972 at Oldwick, N.J., and a voucher specimen was deposited at the College of Pharmacy, Rutgers University.

[2] Skelly-B (bp 60–68°), Skelly Oil Co.

[3] PF-254, Brinkmann Instruments Inc., Westbury, N.Y.