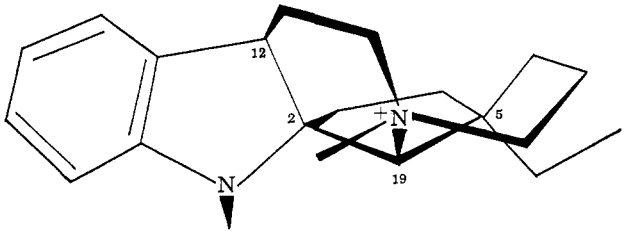
might also apply to the *Schizozygia* alkaloids[8] (*e.g.*, schizozygine (VII)[9]), the only other reported compounds having the vallesamidine (I) skeleton. Vallesamidine is formally a completely reduced member of this series, and it should be noted that both genera belong to the same family, *Apocynaceae*. Whereas *Schizozygia* has yielded[8] alkaloids based on only one structural type, *Vallesia* contains[2] a remarkable variety of skeletons, making this plant a prime candidate for biochemical tracer studies.

Vallesamidine N(b)-methiodide (Chart I)[2] was crystallized from acetone to give monoclinic prisms or needles elongated along the unique axis. The space group is $P2_1$. The unit cell dimensions are: a = 11.977 ± 0.005, b = 12.009 ± 0.006, c = 9.4224 ± 0.0008 Å; γ = 115.95 ± 0.20°; V = 1218.4 Å^3. The density measured by flotation accounts for two alkaloid molecules and two molecules of acetone per unit cell (calcd: 1.353 g/cc; found: 1.347 ± 0.020 g/cc).

Chart I. Three-Dimensional Projection of Vallesamidine N(b)-Methiodide, Showing Correct Absolute Configuration



A total of 6375 diffraction intensities was collected using Mo Kα radiation. Averaging according to Friedel's law gave 3040 unique reflections, of which 2507 were nonzero. The unique iodine position was determined from a sharpened three-dimensional Patterson function. Refined iodine parameters were used to calculate a three-dimensional electron density function, which revealed all of the alkaloid atoms (except hydrogen). After full-matrix least-squares refinement with all of the data the discrepancy factor ($R = \Sigma(||F_o| - |F_c||)/\Sigma|F_o|$) was 0.098.

The partial structure which includes only the iodine atoms is centrosymmetric, giving rise to a false mirror plane at z = 0.25. Eight of the light atoms were determined to lie in or near this plane; the rest had a twofold ambiguity in z, so that both mirror images of the structure were obtained concomitantly. A probable single image was derived from consideration of bond distances and angles. This was confirmed independently to be the statistically most probable set of atom positions, as determined by a superposition analysis of the sharpened Patterson function in which the interatomic vectors involving an iodine atom and those between symmetry-related C, N, and O atoms were approximately removed. This objective method of sorting out atoms related by pseudo-symmetry was very useful in this case and will be described in a subsequent publication.

For the determination of the absolute configuration the raw data were re-averaged to take into account anomalous dispersion. Of 5744 unique reflections, 4595 were nonzero, including 1925 anomalous dispersion pairs. One cycle of refinement was run with each enantiomer using the nonzero data. The imaginary component of the iodine anomalous dispersion was included in the structure factor calculations. The enantiomer with carbon 5 in the R configuration (shown in I) had a significantly lower R factor and is clearly the correct one. A three-dimensional projection is shown in Chart I.

Attention should be called to the mass spectrum (see ref 2) of vallesamidine (I), which displays m/e 124 as the base peak, as well as a significant M − 28 peak, two features which are considered[5,10] to be characteristic of the aspidospermine (III) skeleton and which led us originally[2] to the working hypothesis that vallesamidine was simply a stereoisomer of II. A rationalization of these data will be provided in our detailed manuscript.

Acknowledgment. We wish to thank Dr. Ted E. Hopkins for assistance in collecting the diffraction data. We gratefully acknowledge research support from the Advanced Research Projects Agency through the Stanford Center for Materials Research (Grant SD-87), the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grants 407-G and 3068-A5), and the National Institutes of Health (Grant GM-11309).

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(9) In contrast to structures I–IV, no absolute configuration is implied in VII.

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Homogeneous 1,4 Addition of Hydrogen Catalyzed by Tricarbonyl(arene)chromium Complexes

Sir:

Tayim and Bailar[1] elucidated the mechanism of homogeneous hydrogenation of polyolefins catalyzed by platinum- and palladium–$SnCl_3$ complexes. Among the various mechanisms discussed by Halpern[2] for the activation of hydrogen, formation of dihydride intermediates has been recognized in the catalytic reactions of soluble triphenylphosphine complexes of iridium[3] and rhodium.[4] We recently discovered that tricarbonyl(arene)chromium complexes catalyze the selective hydrogenation of methyl sorbate (*trans*-2,*trans*-4-hexadienoate) to methyl 3-hexenoate.[5] We now have evidence, based on deuterium tracer studies, that this reduction proceeds by 1,4 addition. A dihydride complex is implicated as an intermediate. Additional ob-

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servations provide further insight on the mechanism of homogeneous hydrogenation.

Reduction of methyl sorbate with pure deuterium[6] catalyzed by tricarbonyl(methyl benzoate)chromium yielded methyl dideuterio-3-hexenoate as the major product (Table I). Nondeuterated and monodeuterated species in the product were either absent or negligible. In a partially reduced sample the methyl sorbate (46%) contained no deuterium, whereas the methyl 3-hexenoate (54%) had two deuterium atoms per molecule. In reduction with mixtures of H_2 and D_2 the H_2–D_2 exchange was small (4–6%). The product showed a significant isotopic discrimination. Nondeuterated and dideuterated species were present in a 2:1 ratio compared to an H_2:D_2 ratio of 1.3–1.4:1 in the gas system. Monodeuterated 3-hexenoate corresponded approximately to the small amount of HD formed by exchange. When the tricarbonylchromium complex was treated with a mixture of H_2 + D_2 in the absence of methyl sorbate, the H_2–D_2 exchange increased about twofold.[7] Therefore, the tricarbonyl(methyl benzoate)chromium complex alone is an effective catalyst for H_2 activation and H_2–D_2 exchange. However, in the presence of a reducible conjugated diene, hydrogen (deuterium) addition predominates over exchange.

Table I. Mass Spectrometric Results[a]

Gas system	Gas phase, mole % H_2	HD	D_2	Methyl 3-hexenoate, isotopic distribution,[b] mole % d_0	d_1	d_2	d_3	d_4	d_{av}
H_2	99.6	0.1	0.3	97	1.9	1.1			0.04
D_2		1.1	98.9	2.6	2.6	91	1.9	1.9	2.0
D_2		1.1	98.9	3.0	0.0	94	2.1	0.9	2.0
H_2 + D_2	56.1	4.4	39.5	61	6.2	32	0.4	0.4	0.72
H_2 + D_2	53.0	5.9	41.1	62	4.7	32	0.8	0.5	0.74

[a] Analyses on gas and liquid phases after reduction of methyl sorbate to methyl 3-hexenoate.[6] Analyses on a Bendix Model 12 time-of-flight mass spectrometer at 50 V with a heated inlet system at 150°. Methyl 3-hexenoate in the products was purified through a gas–liquid partition chromatograph connected in tandem to the mass spectrometer (F & M chromatograph Model 720, column 8 ft, 0.25 in., 25% diethylene glycol succinate on Chromosorb W 60–80 mesh, 90°). Analyses by glpc showed that the concentration of methyl 3-hexenoate in the final reaction mixtures varied from 94 to 96%. (Other components included 2-hexenoate, 2–3%; 4-hexenoate, 0.2–0.5%; hexanoate, 0.5–1.0%.) [b] Data corrected for ^{13}C abundance but not for contamination in the H_2 and D_2 used. d_0, d_1, etc. = number of deuterium atoms per mole of ester; d_{av} = average number of deuterium atoms per mole of ester.

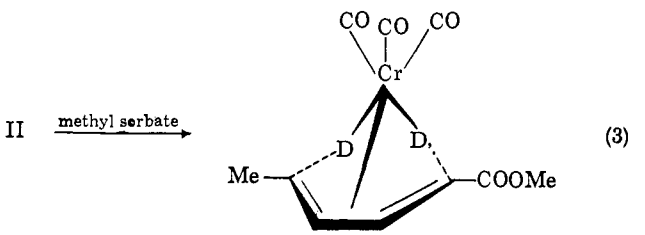
Proton and deuterium nmr[8] established unequivocally that the product from deuterium reduction was methyl 2,5-dideuterio-3-hexenoate (IV).[9] Each resonance due to the allyl proton on C-5 (τ 7.9) and to the α-methylene proton on C-2 (τ 6.9) decreased in relative intensity from two in the product reduced with H_2 to one in the product reduced with D_2. The areas of the other signals remained the same. The deuterium resonance spectrum showed two signals of approximately equal intensities. A doublet at 65.5 cps corresponds to the α-methylene proton resonance (C-2). The splitting of this signal (J = 3 Hz) is too large to be derived from the vicinal olefinic proton. It is probably due to geminal coupling between D and H. The second deuterium resonance is a broad multiplet and its shift (81.5 cps) corresponds to the allyl proton resonance (C-5).

Free methyl benzoate was detected during the course of hydrogenation and in the final product. Rate curves also showed that hydrogenation was preceded by an induction period of 1 hr. These results may be interpreted in terms of a mechanism involving dissociation of the catalyst complex as the initial and most probable rate-determining step (reaction 1).

$$\text{PhCOOMe–Cr(CO)}_3 \rightleftharpoons \underset{\text{I}}{\text{PhCOOMe}} + [\text{Cr(CO)}_3] \quad (1)$$

$$\text{I} + \text{D}_2 \rightleftharpoons \underset{\text{II}}{[\text{D}_2\text{Cr(CO)}_3]} \quad (2)$$

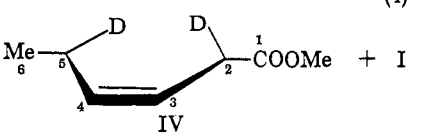
$$\text{I} + \text{H}_2 \rightleftharpoons \underset{\text{IIa}}{[\text{H}_2\text{Cr(CO)}_3]} \quad (2a)$$



(3)

III

(4)



IV

The almost exclusive formation of a dideuterated product indicates that a dideuteride (dihydride) complex intermediate is formed as a second step in the hydrogenation (reaction 2). Although II and IIa have not been detected, this step is assumed by analogy with the better known dihydride complexes involved in the hydrogenations catalyzed by $IrCl(CO)(PPh_3)_3$[3] and $RhCl(PPh_3)_3$.[4] The catalytic H_2–D_2 exchange reaction forming HD would involve $[HDCr(CO)_3]$ as an intermediate.

The localization of deuterium on C-2 and C-5 of IV suggests an intermediate (III) involving 1,4 addition (reaction 3) to a cisoid-complexed diene system containing and transferring deuterium (hydrogen). *cis* addition and simultaneous deuterium (hydrogen) transfer are implied in the formation of IV (reaction 4).

The kinetic data showed a small inverse isotopic effect in the rates of reduction with either H_2 or D_2 alone ($k_H/k_D \sim 0.9$).[11] Yet, when a mixture of these

(6) Hydrogenations were carried out in a 150-ml Magne Dash autoclave with a mixture of 9.5 mmol of methyl sorbate, 0.5 mmol of methyl benzoate–$Cr(CO)_3$, and 50 ml of cyclohexane at 160° and 15–21 atm. Under these conditions methyl sorbate was completely reduced to methyl hexenoate within 3–4 hr.

(7) The amount of HD formed under the same conditions[6] was 12.5% after 4 hr and 20.0% after 7 hr.

(8) Proton nmr run at 60 MHz (Varian A-60) in $CDCl_3$; tetramethylsilane internal reference. Deuterium nmr run at 15.4 MHz (Varian HA-100) in $CDCl_3$ used as internal reference.

(9) The *cis* configuration of the double bond in hydrogenated and deuterated IV is deduced from the absence of absorption at 970 cm^{-1} due to isolated *trans* unsaturation.[10]

(10) A. F. Mabrouk, H. J. Dutton, and J. C. Cowan, *J. Amer. Oil Chem. Soc.*, **41**, 153 (1964).

(11) This inverse isotopic effect is of the same magnitude as that observed[4] in the hydrogenation catalyzed by $RhX(PPh_3)_3$. This effect

gases was used, a significant isotopic discrimination was observed in favor of the formation of the hydrogenated product over the deuterated product (Table I). This result indicates that in reactions 2 and 2a the formation of dihydride IIa is preferred over the formation of dideuteride II, and neither reaction is rate controlling.

That no exchange occurs before addition is shown by the absence of deuterated species in partially reduced sorbate. This result and the stereochemical requirement of the suggested intermediate III are consistent with the unusually high selectivity of this catalyst system.

The tricarbonylchromium complex should have practical utility in tracer studies to label olefins specifically with deuterium or possibly tritium.

was first interpreted in terms of the transfer step being rate determining and was explained by considering differences in the activated complex.[4a] Later when solvent displacement was considered rate determining, secondary isotopic effects were invoked.[4b]

(12) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Mention of firm names or trade products is made for information only and does not constitute endorsement by the U. S. Department of Agriculture.

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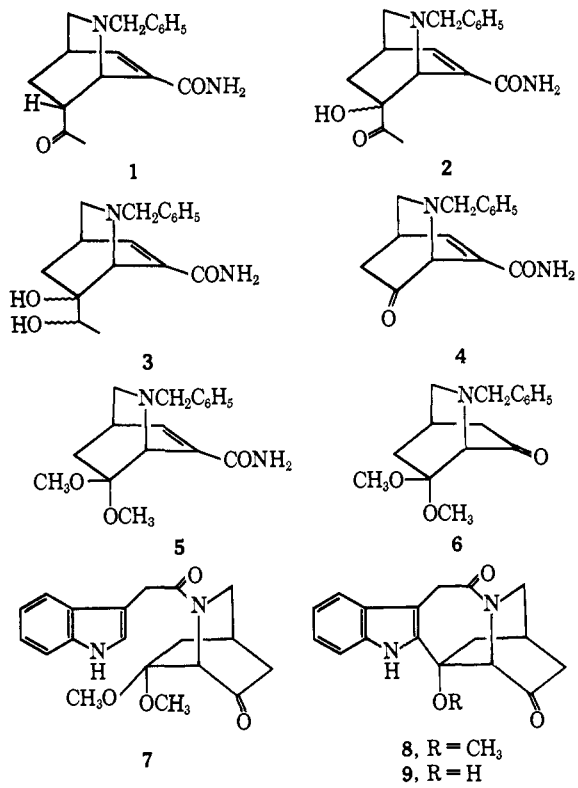
The Total Synthesis of Velbanamine

Sir:

The oncolytic agents vinblastine and vincristine[1,2] are "dimeric" alkaloids containing a pentacyclic indoline and a tetracyclic indole moiety. Fragmentation into these structural units is brought about readily by reduction in acidic media which in the case of vinblastine gives desacetylvindoline[3] and velbanamine (**14**).[4] These fragments are obvious intermediates in a synthesis of vinblastine, and we now describe the first total synthesis[5] of velbanamine (**14**).

Oxygenation[6] of the isoquinuclidine **1**[7] in *t*-butyl alcohol–monoglyme saturated with potassium *t*-butoxide at −20° gave the hydroxy ketone **2**,[8] mp 156–158°. The corresponding diol **3**, mp 182–183°, prepared by reduction of the hydroxy ketone with sodium borohydride, was cleaved with sodium metaperiodate in aqueous methanol to give the ketone **4**, mp 109–112° (ethyl acetate solvate). The latter was transformed to the ketal **5**, mp 163–165°, by treatment with a mixture of methyl orthoformate and methanol in the presence of *p*-toluenesulfonic acid at reflux during 24 hr. Hofmann reaction[9] followed by hydrolysis with sodium carbonate in methanol–water gave the ketone **6**, mp 121–123°. Hydrogenolytic debenzylation of the hydrochloride of **6** over a palladium catalyst proceeded smoothly, and condensation of the crude secondary amine hydrochloride with sodium indoleacetate in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[10] in water gave the amide **7**, mp 106–112° (benzene solvate). Cyclization with 1.1 equiv of *p*-toluenesulfonic acid in refluxing benzene[11] during 30 min yielded the pentacyclic methoxy ketone **8**, mp 282–284°. In agreement with structure **8** the nmr spectrum ($CDCl_3$) displayed an AB quartet centered at δ 3.94, a one-proton singlet at 4.83, and a three-proton singlet at 3.09 which were assigned to the methylene group adjacent to the indole ring, the bridgehead hydrogen atom next to the amide nitrogen, and the methoxy group, respectively.



Cleavage of the methyl ether **8** in acetic acid containing 6% perchloric acid[12] at room temperature during 24 hr furnished the hydroxy ketone **9**, mp 262–264°. A solution of the aldol **9** in *t*-butyl alcohol containing potassium *t*-butoxide displays ultraviolet absorption at 350 mμ indicating the presence of the anion derived from the 2-acylindole **10**. Quenching with acetic acid gave a solution of the unstable 2-acylindole **10** (uv absorption at 316 mμ) which was buffered at pH 6 and sodium borohydride was added. Work-up followed by chromatography on silica gel gave the diol **11**, mp 272–275°, convertible to the alcohol **12**, mp 270–273°, by reduction with tin and

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