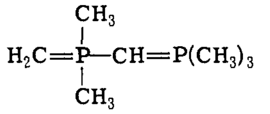
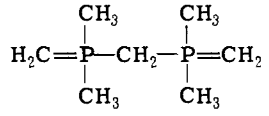
$(CH_3)_3P{=}C{=}P(CH_3)_3$

5



5a

$H_2C{=}\overset{CH_3}{\underset{CH_3}{P}}{-}CH{=}P(CH_3)_3$



5b

$H_2C{=}\overset{CH_3}{\underset{CH_3}{P}}{-}CH_2{-}\overset{CH_3}{\underset{CH_3}{P}}{=}CH_2$

(>120°) is supposed to be essential for an effective delocalization of the high negative charge into the P-C-P π-system:

$$(CH_3)_3P{=}C{=}P(CH_3)_3 \longleftrightarrow \begin{matrix}(CH_3)_3\overset{+}{P}{-}\underline{C}^{-}{=}(CH_3)_3\\ (CH_3)_3P{=}\underline{C}^{-}{-}\overset{+}{P}(CH_3)_3\end{matrix} \longleftrightarrow (CH_3)_3\overset{+}{P}{-}\underline{C}^{2-}{-}\overset{+}{P}(CH_3)_3$$

Addition of excess ethereal hydrochloric acid to a solution of **5** in ether affords the bisphosphonium salt **6**, $[(CH_3)_3PCH_2P(CH_3)_3]Cl_2$, which is easily characterized. With 1 equiv of HCl only the monochloride **4** is obtained.

Other chemical reactions and the coordination chemistry of **5** are under investigation.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft for their support of this investigation, Farbwerke Hoeschst, Werk Knapsack, for chemicals, and Dr. F. H. Köhler for the ^{13}C NMR spectra.

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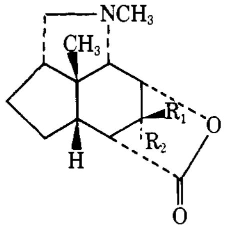
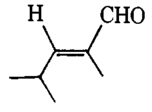
Diene Isomerization in a Diels-Alder Reaction. The Synthesis of 8-*epi*-Dendrobine

Sir:

Dendrobine (**1a**) is representative of the unique lactone alkaloids produced by *Dendrobium nobile* Lindl, having both skeletal structure and pharmacological properties similar to those of picrotoxin.[1] Several total syntheses of dendrobine have been reported.[2] We now report the synthesis of an epimer of dendrobine (**1b**) resulting from diene isomerization in an intramolecular Diels-Alder reaction.



1a, $R_1 = CH(CH_3)_2$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH(CH_3)_2$



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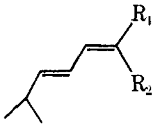
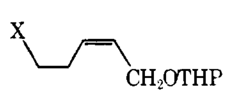


3a, $R_1 = CH_3$; $R_2 = CH_2OH$
b, $R_1 = CH_3$; $R_2 = CHO$
c, $R_1 = CH_3$; $R_2 = CH_2CN$
d, $R_1 = CH_2OH$; $R_2 = CH_3$



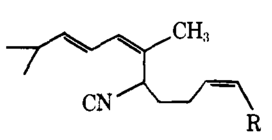
4a, $X = OH$
b, $X = Br$
c, $X = I$

Directed aldol condensation[3] of isobutyraldehyde and ethylidene-*tert*-butylamine produced trans aldehyde **2** (50%). Sequential reaction of **3** at −70° with ethylidenetriphenylphosphine, butyllithium, and formaldehyde gas[4] gave a 16:1 mixture of dienols **3a** and **3d** (40%); assignment of configuration was based on a coupling constant of 14 Hz for the disubstituted double bond protons and a chemical shift for the aldehyde proton in **36** of 10.27 ppm as compared with 9.51 ppm for the aldehyde obtained from the minor isomer.[5] Reaction of **3a** with methyllithium-*p*-toluenesulfonyl chloride-lithium chloride[7] followed by heating the crude chloride with lithium iodide and cuprous cyanide ($HMPA$-H_2O, 60°, 16 hr) gave the corresponding nitrile **3c** (49%).

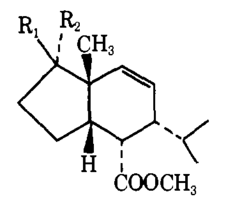
Alcohol **4a** was prepared in 54% yield by treating the sodium salt of propargyl THP ether with ethylene oxide, followed by Lindlar[8] reduction of the triple bond. Conversion of **4a** via **4b** (Ph_3PBr_2, pyridine, 83%) to the iodo compound **4c** (NaI, acetone, 88%) proceeded smoothly. Rapid addition of **4c** in HMPA-THF (−25°) to a solution of the anion of **3c** in THF at −25° (prepared from **3c** and lithium isopropylcyclohexylamide) afforded the triene **5a** in 80% yield following dry column chromatography. High pressure liquid chromatography (HPLC) showed that **5a** was homogeneous.

Hydrolysis of **5a** (H_2SO_4-H_2O, THF) gave the alcohol **5b** (56%) which was directly oxidized to aldehyde **5c** ($CrO_3\cdot$pyr, CH_2Cl_2, 84%).[9] HPLC analysis revealed that **5b** and **5c** were contaminated with ~15% of the trans allylic alcohol and trans aldehyde, respectively. Oxidation[10] of **5c** ($NaCN$-$AcOH$-MnO_2, MeOH) followed by preparative HPLC gave pure triene ester **5d** in 40% yield.

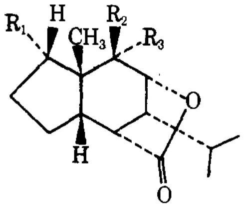
Reflux of **5d** in *o*-dichlorobenzene for 3 days afforded **6a** (25%) and **6b** (24%) after preparative HPLC. Configuration of the cyano group was assigned based on the chemical shift of the 7a-methyl group of the corresponding *N*-methyl amides[2b] (prepared by reaction of the nitrilium salt with water[10]). Thus the methyl group appears at 1.23 ppm in **6c** as compared with 0.97 ppm in **6d**, in accord with Inubushi's assignment of the upfield methyl group to the cis amide-methyl group configuration.[2b] Relative configuration of the remaining asymmetric centers was presumed to follow from the stereochemistry of the starting triene ester—a presump-



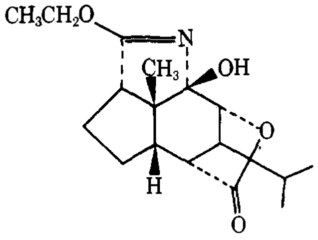
5a, R = CH_2OTHP
b, R = CH_2OH
c, R = CHO
d, R = $COOCH_3$



6a, R_1 = H; R_2 = CN
b, R_1 = CN; R_2 = H
c, R_1 = H; R_2 = $CONHCH_3$
d, R_1 = $CONHCH_3$; R_2 = H
e, R_1 = H; R_2 = CH_2NHCH_3
f, R_1 = H; R_2 = $CH_2N(Cl)CH_3$



7a, R_1 = CN; R_2 = Br; R_3 = H
b, R_1 = CH_2NHCH_3; R_2 = Br; R_3 = H
c, R_1 = CN; R_2 = OH; R_3 = H
d, R_1 = CN; R_2 = R_3 = O



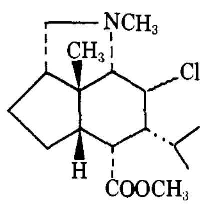
8

tion later found to be erroneous with respect to the isopropyl group (vide infra).

Methyl ester **6a** was cleaved to the corresponding acid (LiI, lutidine, reflux, 12 hr) and converted (Br_2, $NaHCO_3$, H_2O) to bromolactone **7a**, mp 85-86.5°, in 55% overall yield. Conversion of the nitrile to an impure *N*-methylamine[11] was achieved in 25% yield by successive reaction of **7a** with dimethylbromonium hexafluoroantimonate,[12] methanol, and sodium cyanoborohydride.[13] All attempts to cyclize **7b** to the dendrobine skeleton were unsuccessful.

Oxidation of the acid derived from **6a** with *m*-chloroperbenzoic acid gave **7c** (90%), which was oxidized directly (CrO_3-H_2SO_4, acetone, 77%) to ketolactone **7d**, mp 129-130°. Attempted conversion of **7d** to the corresponding methylamine via the nitrilium salt proved unsuccessful due to concomitant destruction of the lactone ring. However, a modified Stephen[14] reduction ($SnCl_2$-HCl, ether, ethanol) carried out on **7d** gave a new compound in 68% yield tentatively assigned structure **8** based on its ir, NMR, and mass spectra. Reaction of **8** with methyl fluorosulfonate followed by sodium cyanoborohydride reduction of the resulting iminium salt gave **1b**, 77%, mp 105.5-108° (ir 2790, 1765 cm^{-1}; NMR ($CDCl_3$) δ 4.66 (d, 1 H, J = 5 Hz), 2.45 (s, 3 H), 0.98 (two doublets, 6 H, J = 6 Hz); mass spectrum calcd for $C_{16}H_{25}O_2N$ 263.1884, found 263.1881). Spectral and HLPC analysis is revealed that this product was similar but not identical with dendrobine.

Our concern for possible epimerization in the Stephen reduction prompted completion of a parallel route based on cyclization of the pyrrolidine ring prior to lactone formation. Thus, cyanoester **6a** was converted to **6e** (54%) by sequential reaction with dimethylbromonium hexafluoroantimonate (SO_2, −78° to −8°), methanol, and sodium cyanoborohydride. Conversion of **6e** to *N*-chloramine **6f** (NaOCl, H_2O-CH_2Cl_2) followed by reaction of **6f** with $TiCl_3$[15] (H_2O-ACOH, −5°) gave the crude cyclized amine **9**. This crude product was treated with lithium iodide-lutidine (reflux, 11 hr) to give **1b** (45%), different from dendrobine but identical with that prepared by the above described route.



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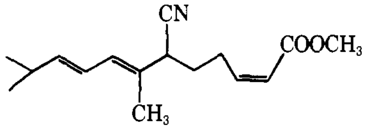

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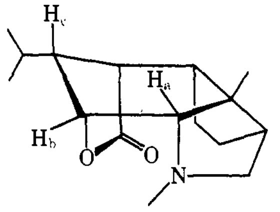
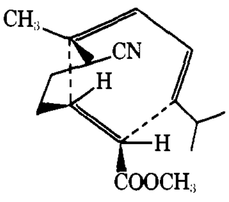
All chemical and spectral data suggested that the carbo skeleton of **1b** was the same as that of dendrobine. Configuration of the pyrrolidine ring relative to methyl is based o NMR analysis of the related amides (vide supra). The coupling constant J_{ab} = 4 Hz in **1b** compares favorably wit that of dendrobine (J_{ab} = 3 Hz) and is in accord with tha predicted for H_a cis to H_b. This in turn establishes the configuration of the lactone ring "cis" to the pyrrolidine ring In **1b**, however, $J_{bc} \leq 2$ Hz, compared to J_{bc} = 5 Hz fo dendrobine. This value for **1b** is in accord with Hb cis to H_c whereas H_b is trans to H_c in dendrobine. Thus, **1b** differs from dendrobine in the configuration of the isopropyl group.

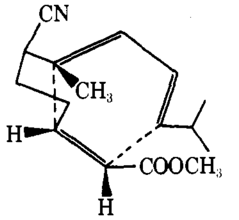


1b

An examination of the transition state for the Diels-Alder reaction suggests a possible explanation for this astonishing result. The triene ester **5d** assumes a severely hindered conformation in the transition state which involves no secondary orbital overlap between diene and ester. Isomerization of the trisubstituted double bond to give **10**, however, leads to a less hindered transition state which allows for secondary orbital overlap. This isomerization with overlap leads to a cyclized product in which the carbon atoms bearing methyl, hydrogen, and carbomethoxy substituents are inverted, which is equivalent to an inversion only at the carbon bearing the isopropyl group.



5d



10

Support for this isomerization was obtained by following the Diels-Alder reaction via HPLC. In addition to the peaks for **5d**, **6a**, and **6b**, a new uv-absorbing peak appeared close to **5d** which was always ≤10% of the total reaction mixture. Isolation of this compound by preparative HPLC showed it to be indistinguishable from **5d** in its FT 100 mHz spectrum but different from **5d** by HPLC analysis. These results are consistent with the assignment of structure **10** to this compound.

This unusual rearrangement[16] is presumably based on the fact that the diene portion of **5d** is unable to attain the "cis coplanar" configuration. Prolonged exposure to 170° temperatures eventually causes rearrangement to **10** which is capable of undergoing cyclization.

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Rotational Microviscosity Factor from Intramolecular Dipole–Dipole Contribution and Deuteron Relaxation Time

Sir:

Assuming a model of central spherical solute molecule surrounded by shells of spherical solvent molecules, Gierer and Wirtz[1] have shown that the rotational microviscosity factor f_r is about ⅙ for a pure liquid. Several authors[2-7] have separated the intramolecular dipole-dipole contribution, $(1/T_1)_{\text{dd-intra}}$, from the other contributions to relaxation by studying resonances of two or more nuclei of a given molecule. The experimental values of $(1/T_1)_{\text{dd-intra}}$ tend to disagree with the Bloembergen, Pound, and Purcell (BPP) theory[8] or the BPP theory modified to include the microviscosity factor $f_r = 1/6$. Nevertheless, a comparison of the experimental values with the calculated values enables a direct determination of f_r.

Glasel[9] has shown that, instead of the commonly accepted value of $f_r = 1/6$ for several liquids, $f_r = 1/12$ gives a better agreement with the experimental deuteron relaxation results. The values of f_r for several liquids calculated using $(1/T_1)_{\text{dd-intra}}$ and deuteron relaxation data are presented in this note.

Table I. Published Values of Density, Viscosity, and Deuteron Quadrupole Coupling Constant in the Perdeuterated Analog of the Given Liquid at 25°C

Liquid	Mol wt	Density d (g/cm³)	Viscosity η (cP)	$(e^2qQ/h)_D$ (kHz)
CH_2I_2	267.87	3.307[a]	2.590[a]	176[e] (CD_2I_2)
CH_2Br_2	173.86	2.4815[a]	0.966[a]	172[e] (CD_2Br_2)
CH_2Cl_2	84.94	1.316[a]	0.430[a]	170[f] (CD_2Cl_2)
C_6H_6	78.11	0.873[b]	0.605[b]	183[g] (C_6D_6)
$C_6H_3D_3$	81.11	0.873[b]	0.605[b]	183[g] (C_6D_6)
C_6H_5Br	157.02	1.485[c]	1.075[c]	175[h] (C_6D_5Br)
CH_3CN	41.05	0.776[d]	0.345[d]	171[g] (CD_3CN)

[a] V. Griffing, M. A. Cargyle, L. Corvese, and D. Eby, *J. Chem. Phys.*, 58, 1054 (1954). [b] See ref 12 pp 140, 141. [c] See ref 12, pp 173, 174. [d] See ref 13, Vol. 3, p 28, and ref 7, pp 117, 118. [e] Estimated. [f] See ref 14. [g] See ref 15. [h] See ref 2.

In the limit of extreme narrowing, the nuclear spin-lattice relaxation time, T_1, due to quadrupolar coupling is given by

$$\left(\frac{1}{T_1}\right)_q = \frac{3}{10}\pi^2 \frac{2I+3}{I^2(2I-1)} \left(\frac{e^2qQ}{h}\right)^2 (\tau_c)_q \qquad (1)$$

where e^2qQ/h is the quadrupole coupling constant and $(\tau_c)_q$ is the reorientational correlation time.

Assuming that the contribution to $(1/T_1)_{\text{dd-intra}}$ arises from interactions between identical spins (I_j, I_j) on the same molecule and the interactions between non-identical spins (I_j, I_k) on the same molecule, then $(1/T_1)_{\text{dd-intra}}$ for spin $I_j = 1/2$ nuclei is given by

$$\left(\frac{1}{T_1}\right)_{\text{dd-intra}} = \hbar^2\gamma^2{}_j \left[\frac{3}{2}\gamma^2{}_j \sum \langle r^{-6}{}_{jj}\rangle + \frac{4}{3}\sum I_k(I_k+1)\gamma^2{}_k\langle r^{-6}{}_{jk}\rangle\right](\tau_c)_{\text{dd-intra}} \qquad (2)$$

where γ_j and γ_k are the gyromagnetic ratios of spins j and k, respectively, r_{jj} is the distance between two identical spins, r_{jk} is the distance between two nonidentical spins and $(\tau_c)_{dd}$ is the correlation time. It is assumed that $(\tau_c)_{\text{dd-intra}}$ is very much shorter than the Larmor period.

Since $(1/T_1)_q$ and $(1/T_1)_{\text{dd-intra}}$ are intramolecular effects which depend in the same way on molecular reorientation, $(\tau_c)_q$ can be assumed to be equal to $(\tau_c)_{\text{dd-intra}}$ and is given by[1,8]

$$(\tau_c)_q = (\tau_c)_{\text{dd-intra}} = \frac{4}{3}\pi f_r\,\eta\,\frac{a^3}{kT} \qquad (3)$$

for a rigid molecule of radius a· η is the coefficient of viscosity. Assuming hexagonal close-packed liquid structure, the radius a is given by

$$\frac{4}{3}\pi a^3 = 0.74\,\frac{M}{dN} \qquad (4)$$

where M = molecular weight, d = density, N = Avogadro's number, and 0.74 is the filling factor.

Combining eq 3 and 4

$$(\tau_c)_q = (\tau_c)_{\text{dd-intra}} = 0.74\,\frac{M\eta}{kTdN} f_r \qquad (5)$$

Measurements of deuteron T_1 in oxygen-free samples of CD_2I_2 and CD_2Br_2 were made at a frequency of 4 MHz using pulsed NMR techniques.[10] $(1/T_1)_{\text{dd-intra}}$ values for CH_2I_2 and CH_2Br_2 were obtained by measuring proton T_1 as a function of proton concentration in oxygen-free mixtures of CH_2I_2-CD_2I_2 and CH_2Br_2-CD_2Br_2. Oxygen was removed from the samples by the freeze-pump-thaw technique described in an earlier paper.[11] For all other liquids $(1/T_1)_q$ and $(1/T_1)_{\text{dd-intra}}$ values were taken from the published data.

The values of density, viscosity, and deuteron quadrupole coupling constant in the perdeuterated analog of each liquid are shown in Table I. The values of f_r calculated using eq 1,