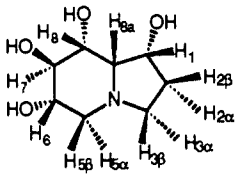
(m) cm^{-1}; HRMS (EI, 70 eV) calcd for $C_8H_{15}NO_4$ 189.1001, found 189.1008. ^{1}H and ^{13}C NMR, and TLC (multiple solvents) were identical with an authentic sample (Sigma).

(1*R*,6*S*,7*S*,8*R*,8a*S*)-1,6,7,8-Tetrahydroxylndolizidine ((+)-1, 8a-Diepicastanospermine, 34). A solution of 0.165 g (0.359 mmol) of (1*R*,6*S*,7*S*,8*R*,8a*S*)-1-hydroxy-6,7,8-tris(benzyloxy)indolizidine and 0.020 g of 10% Pd/C in 4 mL of methanol and 8 drops of concentrated HCl was hydrogenated and purified as for **1** (the second treatment with Amberlite resin was not necessary for this compound), yield 0.054 g (79%), pale yellow oil which crystallizes upon standing at room temperature



NMR assignments are based on ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra:[41] ^{1}H NMR (500 MHz, D_2O, TSP) δ 4.59 (ddd, 1 H (H_1), J = 7.4, 5.0, 2.5 Hz), 4.18 (apparent t, 1 H (H_8), J = 4.3 Hz), 3.92 (apparent t, 1 H (H_7), J = 5.1 Hz), 3.74 (apparent q, 1 H (H_6), J = 5.1 Hz), 3.08 (m overlapping dd at 3.06, 1 H ($H_{3\alpha}$), 3.06 (dd, 1 H ($H_{5\alpha}$), J = 11.6, 5.3 Hz), 2.64 (dd, 1 H ($H_{5\beta}$), J = 11.9, 3.1 Hz), 2.55 (apparent t, 1 H (H_{8a}), J = 4.3 Hz), 2.40 (apparent q, 1 H ($H_{3\beta}$), J = 9.4 Hz), 2.30 (dddd, 1 H ($H_{2\beta}$), J = 14.1, 8.0, 7.4, 2.1 Hz), 1.79 (dddd, 1 H ($H_{2\alpha}$), J = 14.1, 9.0, 9.0, 2.5 Hz); DEPT (125 MHz, D_2O, TSP) δ 75.7 (C_1), 73.5 (C_8), 73.4 (C_7), 72.4 (C_6), 67.3 (C_{8a}), 56.8 (C_5), 54.8 (C_3), 35.2 (C_2); IR (thin film) 3354 (br s) 2932 (m), 2813 (m), 1115 (m), 1062 (m) cm^{-1} MS (EI, 70 eV) *m/e* (relative intensity) 189 (1.5), 171 (1.6), 154 (1.2), 145 (21), 128 (8), 116 (7), 100 (14), 98 (14), 86 (100), 82 (38), 72 (23), 68 (19), 58 (55); HRMS (EI, 70 eV) calcd for $C_8H^{15}NO_4$ 189.1001, found 189.1012. An analytical sample was prepared by recrystallization from acetone/hexane to give clear colorless needles: mp 140–141 °C; $[\alpha]^{28}_D$ −8.8, $[\alpha]^{27}_{577}$ −3.4, $[\alpha]^{27}_{546}$ +7.4, $[\alpha]^{27}_{435}$ +5.6, $[\alpha]^{27}_{405}$ +26.6 (*c* 0.46, CH_3OH). Anal. Calcd for $C_8H^{15}NO_4$: C, 50.77; H, 7.99; N, 7.40. Found c, 50.58; H, 8.08; N, 7.22.

Acknowledgment. Partial funding for this project from the National Institutes of Health (Grant No. NS-25401 and a Career Development Award to A.R.C.) is gratefully acknowledged. Optical rotations and FT-IR spectra were obtained on instruments purchased with funds provided by NSF. We thank Professors Thomas M. Harris for a generous sample of authentic (−)-swainsonine, David J. Hart for copies of spectra of swainsonine, Bruce Ganem for copies of spectra of castanospermine and 1-epicastanospermine, Larry E. Overman and Christopher S. Foote for helpful discussions, and ICN for a generous donation of silica gel.

Supplementary Material Available: Experimental and spectral data for the preparation of the chiral diamines and reduction procedures listed in Table I, ^{1}H–^{1}H COSY spectrum for **1**, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectra for **26** and **34**, DNOE data for **34** (10 pages). Ordering information is given on any current masthead page.

Expansolides A and B: Tetracyclic Sesquiterpene Lactones from *Penicillium expansum*

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Contribution from the Laboratoire de Chimie, URA CNRS 401, Muséum National d'Histoire Naturelle, 63, rue Buffon, 75005 Paris, France, and Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, Cedex, France. *Received April 19, 1990*

Abstract: Two isomeric sesquiterpene lactones, expansolides A and B, have been isolated from a culture of the fungus *Penicillium expansum* and their structures elucidated from a spectroscopic study including IR, MS, NMR, and X-ray crystallography.

Introduction

Penicillium expansum ranks as one of the most common *Penicillium* species on various rotting substrates and is a widely distributed soil fungus.[1] It displays an antagonistic activity in vitro toward various bacteria and fungi.[2] As part of our interest in investigating fungi with antagonistic properties as a source of antifungal products, we examined an isolate of *P. expansum* collected on a fruit. From the ethyl acetate extract of the culture filtrate, we isolated in addition to the known patuline,[3-5] which was responsible for the antifungal properties, a mixture of two new compounds for which we suggest the names expansolides A and B. Each of them, obtained as a pure compound by column chromatography, spontaneously gave rise to a mixture, in various proportions, of both compounds when kept in solution.

Results and Discussion

The molecular formula of expansolide A, **1**, was determined from the HR-MS spectrum as $C_{17}H_{22}O_5$; the CI-MS showed the pseudomolecular $[M + H]^+$ ion at m/z = 307. The loss of a molecule of acetic acid leading to the ion m/z = 246 suggested the involvement of an acetyl group. Its IR spectrum was indicative of two ester carbonyls, as strong absorptions were observed at 1778 and 1743 cm^{-1}. The ^{13}C NMR spectrum exhibited 17 carbon atoms (Table I). Deshielded ^{13}C NMR resonances at δ 113.8 (C), 170.3, and 178.9 indicated the presence of a ketal and two ester functionalities, respectively. A ^{13}C NMR *J*-modulated experiment revealed 12 carbons attached to a total of 22 hydrogen atoms. From the ^{1}H–^{1}H COSY and ^{1}H–^{1}H LR COSY spectra, the protons could be classified into three spin-relaying groups: (i) CH_3CHCH_2–, (ii) >CCH_2CCH_2O–, (iii) –$CHCH_2CHCH_2CH$-(OAc)C=CH_2. Connectivities between these substructures were established by a 2D-INADEQUATE experiment in the range δ_C 10–80 and resulted in the determination of the plane structure of the

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Table I. ^{13}C and ^{1}H NMR Spectral Data of Expansolides A, **1**, and B, **2** (^{13}C, 75.47 MHz; ^{1}H, 300.13 MHz; $CDCl_3$; TMS as Internal Standard)

	1	**2**		**1**			**2**		
C no.	δ_C	δ_C		δ_H	mult	J (Hz)	δ_H	mult	J (Hz)
1	178.9	178.3	(C)						
2	34.7	35.8	(CH)	2.914	ddq	11.4; 8.2; 7.2	2.727	ddq	9.3; 5.6; 7.3
3a	39.8	39.1	(CH_2)	2.478	dd	13.0; 8.2	2.526	dd	13.5; 9.3
3b				1.998	dd	13.0; 11.4	2.054	dd	13.5; 5.6
4	113.8	115.2	(C)						
5a	47.1	47.7	(CH_2)	2.637	d	13.5	2.217	d	13.4
5b				2.278	d	13.5	2.678	d	13.4
6	50.7	50.7	(C)						
7	40.2	40.8	(CH)	2.561	m		2.30	m	
8a	29.6	29.6	(CH_2)	2.306	dddd	10.0; 5.9; 5.8; 2.0	2.29	m	
8b				1.733	d	10.0	1.724	d	9.0
9	51.8	50.8	(CH)	2.782	dd	5.8; 5.6	3.085	dd	5.6; 5.5
10	148.2	147.3	(C)						
11	67.6	67.7	(CH)	5.450	dddd	7.6; 2.3; 1.2; 1.2	5.422	dd(l)	8.1; 2.4
12a	32.8	33.6	(CH_2)	2.403	dddd	15.4; 7.6; 2.1; 2.0	2.341	dddd	15.0; 8.1; 2.1; 2.1
12b				1.883	ddd	15.4; 3.7; 2.3	1.873	ddd	15.0; 3.0; 2.4
13	14.9	16.6	(CH_3)	1.260	d	7.2	1.342	d	7.3
14a	71.6	72.0	(CH_2)	3.791	d	9.8	3.736	d	9.7
14b				3.623	d	9.8	3.766	d	9.7
15a	115.1	116.1	(CH_2)	5.116	dd	1.2; 1.2	5.159	s(l)	
15b				4.982	dd	1.2; 1.2	5.101	s(l)	
16	170.3	170.3	(C)						
17	21.4	21.4	(CH_3)	2.063	s		2.066	s	

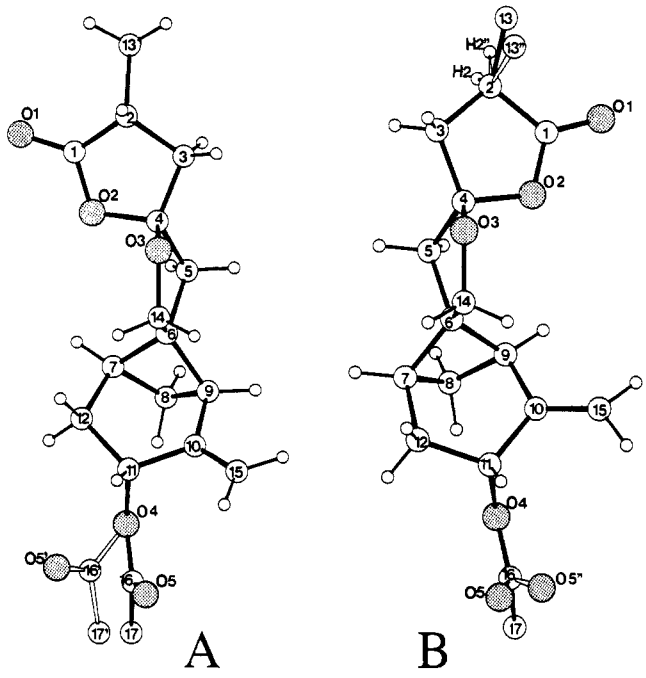
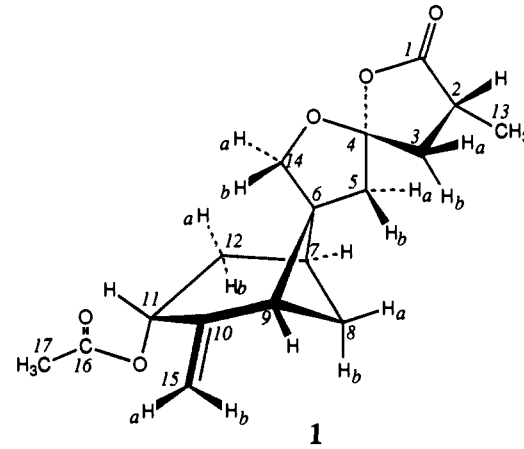


Figure 1. Perspective view of expansolides A, **1**, and B, **2**. Major and minor positions of disordered groups are indicated by black and white bonds, respectively.

molecule. Cross peaks were observed as follows: between C6 and the four carbon atoms C5, C7, C9, and C14; between C12 and both C7 and C11; between C8 and C7 and C9; and finally between C2 and C13 and C3. Carbon atoms 6, 7, 8, and 9 thus formed a cyclobutane ring. The large $^{4}J_{H-H}$ coupling constant value (5.6 Hz) observed between H7 and H9 was in agreement with their relative cis disposition on the opposite corners of a four-membered ring (Table I).[6,7] The signal at δ_H 1.733 was assigned to H8b, as its $^{3}J_{H-H}$ coupling constant values with H7 and H9 were very small (<0.1 Hz), indicative of dihedral angles H8b–C–C–H7 and H8b–C–C–H9 close to 90°.

Information on the relative stereochemistry was deduced from NOE difference experiments. Strong NOE's were observed between $H_3$13 and H3b (7.4%), H2 and H3a (5.6%), H11 and H12a (5.1%), H11 and H15a (3.4%), and H9 and H15b (7.5%) involving a cis mutual disposition of these couples. Significant NOE's were measured between H9 and H14b (1.6%), H9 and H5b (7.0%), and H3b and H5b (6.5%). In summary, the data defined the relative disposition of the rings and led to structure **1** for ex-



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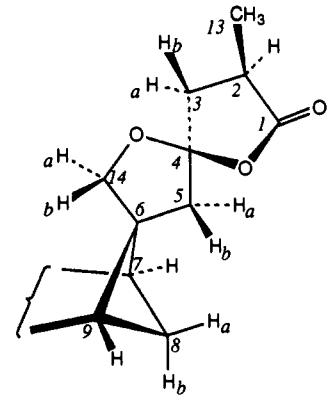

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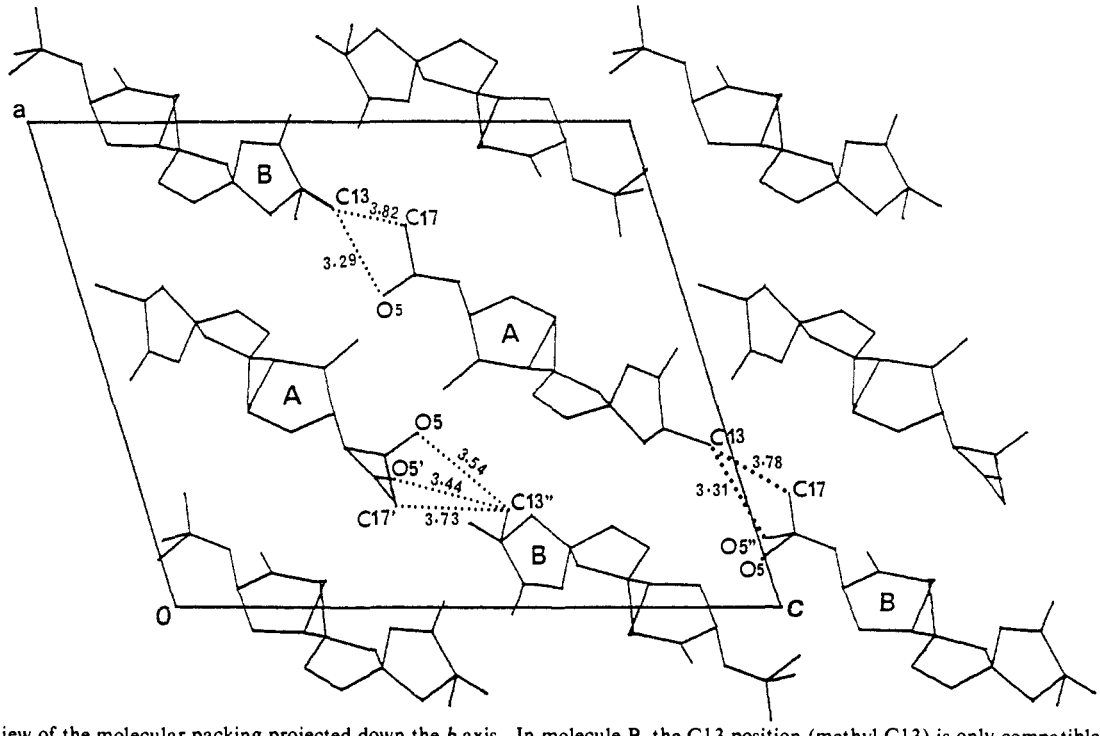

Figure 2. View of the molecular packing projected down the *b* axis. In molecule B, the C13 position (methyl C13) is only compatible with the major position of the acetyl group (C17, C16, O5) of molecule A, while the C13″ position authorizes the minor and the major positions of that group. In molecule A, the C17 and the C17′ positions are superimposed.

pansolide A. The acetoxyl group at C11 must be in a quasi-axial orientation, as the geminal proton H11 gave a large ^3J coupling constant (7.6 Hz) with cis H12a and a small one (2.3 Hz) with trans H12b.

Purified expansolide A spontaneously gave rise to a mixture of expansolides A and B; the transformation was prevented by lowering the temperature. The same observation was noticed with purified expansolide B, which also gave the mixture of both compounds and suggested expansolide B to be an isomer of expansolide A. The mass spectra of both compounds were identical; IR as well as NMR spectra were very similar (Table I). Proton connectivities established by ^{1}H-^{1}H COSY and ^{1}H-^{1}H LR COSY data led to the same plane structure as expansolide A. NOE measurements resulted in the same relative stereochemistry for substructures of both compounds. (i) The butyrolactone cycle: strong NOE's were observed between $H_3$13 and H3b (5.6%) and H2 and H3a (5.4%). (ii) The six-membered ring bearing the acetoxyl-group: H11 is cis to H12a (6.4%) and H15a (3.6%), and H9 is cis to H15b (6.0%).

The NOE's between H3a and H5a (2.9%) and between H9 and H5b (4.1%) were essential to determine the stereochemistry at C4 and to define the ring junction that allowed us to distinguish expansolide A from B. Structure **2** was assigned to expansolide B, which is thus the epimer of expansolide A at C4.

Single-crystal X-ray analysis of expansolides supported the ring system proposed from the spectral data. Crystals were obtained by slow crystallization of purified expansolide A from methanol. The crystallographic study clearly established the surprising presence in the crystal of the two epimeric expansolides A and B as the two molecules of the asymmetric unit. Further chromatographic and NMR analysis proved the resultant crystals to be an equimolecular mixture of expansolides A and B. Figure 1 shows the two molecules A, **1**, and B, **2**, in relative configuration with the atom numbering. The six-membered rings only exhibit the same half-chair conformation with identical torsion angles. The C11–O4 bond is axial; the two acetyl groups are disordered in both molecules but, while in molecule A the three atoms C16, O5, and C17 are split (C16–C16′ = 0.93 (3) Å, C17–C17′ = 0.74 (3) Å), the oxygen atom O5 only is split (O5–O5″ = 0.89 (2) Å) in molecule B, with the same twist angle (43.6°). The five-membered rings (O3–C4–C5–C6–C14) showing torsion angles of equal values but opposite signs are in a half-chair conformation with atoms C4 and C5 out of the plane defined by the three other ones.

The lactone ring in molecule A adopts an envelope shape with atom C3 deviated by −0.464 (8) Å from the mean plane of the four other atoms and the methyl group C13 in an equatorial position, at −0.79 (1) Å from that plane. This ring in molecule B appears as flattened (torsion angle values between 2 and 6°). This is the consequence of the very large thermal motion of the atoms C3, C4, O2, and O3 contrary to the molecule A, so that, in molecule B, two extreme positions are observed for the methyl group: C13 as equatorial and C13″ as axial, which are 0.59 (2) and 1.55 (3) Å from the lactone plane, respectively (C13–C13″ = 1.19 (3) Å, C13–C2–C13″ = 44.5 (1)°).

A view of the molecular packing, projected down the *b* axis, is shown in Figure 2. It can be seen that molecules A alternate with molecules B in rows parallel to the *ac* diagonal, the disordered groups being opposite each other. Close contacts, C13B–O5A (3.29 Å), C13″B–O5A (3.54 Å), C13″B–O5′A (3.44 Å), and C13A–O5″B (3.31 Å), ensure an efficient packing of the molecules.

Expansolides A and B for which we assigned the structures **1** and **2**, respectively, showing relative configuration, represent a new sesquiterpene skeleton. Insofar as their biosynthesis is concerned, it is suggested that they are generated from multiple cyclizations of a farnesyl-type compound, leading to a four- and a six-membered carbon ring and two five-membered heterocyclic rings.

Experimental Section

General Methods. ^{1}H 300.13-MHz and ^{13}C 75.47-MHz NMR spectra were performed on an AC 300 Bruker spectrometer, and INADEQUATE was performed on a WM 500 Bruker. EI and CI MS were obtained with a Nermag Sidar V 3.0 mass spectrometer.

Isolation of Expansolides A and B. *P. expansum* Link (MNHN 3120) was cultivated on a Czapek–Dox medium for 17 days at 27 °C in Roux flasks (72 flasks). The culture was filtered, the culture filtrate (12 L) extracted three times with EtOAc, and the organic phases were evaporated to dryness. The residue (7 g) was dissolved in water (1.5 L) and the aqueous solution extracted with *n*-hexane and then with EtOAc. The hexane extract (1.34 g) was chromatographed over a silica gel 60H column with cyclohexane/EtOAc (3/1); 100 fractions of 0.4 mL were collected. Fractions 25–40 contained expansolide A (580 mg) and fractions 50–65 expansolide B (510 mg). Purity was monitored by TLC (SiO_2, toluene/EtOAc/formic acid (70/40/4)): expansolide A, R_f 0.53;

expansolide B, R_f 0.40. The EtOAc extract was evaporated to dryness, and the residue (1.20 g), crystallized in MeOH, gave pure patuline that was characterized by comparison of its melting point (110 °C) and spectroscopic data with already published values.[3-5]

Expansolide A (1, $C_{17}H_{22}O_5$): Colorless crystals; mp 111-112 °C (MeOH); $[\alpha]^{24}_D$ -67.5° (c = 0.4, $CHCl_3$); IR (KBr; ν, cm^{-1}) 2951, 1778, 1743, 1647, 1444, 1381, 1362, 1345, 1231, 1204, 1132, 1037, 1025, 995, 926, 692, 613; CI-MS (NH_3, HR) m/z 307.1530 $[M + H]^+$, $C_{17}H_{23}O_5$ (calcd m/z 307.1545); EI-MS, m/z (%) 307 ($[M + H]^+$, 16), 262 (18), 246 (19), 218 (8), 217 (6), 200 (4), 187 (5), 182 (6), 180 (6), 173 (5), 155 (11), 154 (10), 134 (28), 117 (29), 115 (25), 91 (100), 77 (23), 69 (29).

Expansolide B (2, $C_{17}H_{22}O_5$): not crystallized; $[\alpha]^{24}_D$ -14.8° (c = 0.5, $CHCl_3$); IR (KBr; ν, cm^{-1}) 2950, 1771, 1737, 1654, 1468, 1442, 1372, 1343, 1245, 1199, 1128, 1045, 990, 970, 925, 766, 691, 605; CI-MS (NH_3) m/z 307 $[M + H]^+$; EI-MS, m/z (%) 307 ($[M + H]^+$, 100), 262 (17), 246 (31), 218 (13), 217 (10), 200 (6), 187 (7), 182 (6), 180 (11), 173 (7), 155 (10), 154 (7), 134 (21), 117 (30), 115 (26), 91 (68), 77 (15), 69 (18).

X-ray crystal analysis: $C_{17}H_{22}O_5$; molecular weight 306.36; crystals obtained by slow crystallization of expansolide A from methanol; monoclinic system, space group $P2_1$; Z = 4 (two epimer molecules in the asymmetric unit: A and B); a = 14.747 (7), b = 6.504 (4), and c = 17.743 (8) Å; β = 108.55 (2)°; V = 1613.4 Å; d_c 1.26 g·cm^{-3}; $F(000)$ = 656; λ (Cu Kα) = 1.5418 Å; μ = 6.7 cm^{-1} (absorption ignored).

Data were collected on a Phillips PW 1100 diffractometer with graphite-monochromated Cu Kα radiation. From the 2969 reflections measured by the θ-2θ scan technique up to θ = 65°, only 1596 were considered as observed and kept in refinement calculations having $I \geq 3\sigma(I)$, $\sigma(I)$ from counting statistics.

The structure was solved by direct methods with the program SHELX86[8] and refined by blocked full-matrix least-squares minimizing the function $\sum w(|F_o| - |F_c|)^2$ with the program SHELX76.[9] Difference Fourier maps showed the methyl group on the lactone ring in molecule B and the acetyl group of each molecule to be disordered. The respective occupancy factors were refined and confirmed to be 0.50 for the two positions of C13B and 0.75 and 0.25 for the major and the minor positions of the acetyl groups in both molecules. Constraints were applied to fix the geometry of the acetyl groups. The hydrogen atoms, except those fixed on the disordered methyl groups not located in difference maps, were introduced in the refinement at theoretical positions (C - H = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.077, R_w = 0.096 (with $R_w = \{\sum w(|F_o| - |F_c|)^2/\sum wF_o^2\}^{1/2}$ and $w = 1/\sigma^2(F_o) + 0.01305F_o^2$). No residual was higher than 0.33 e Å^{-3} in the final difference map.

Patuline (3): mp 110 °C (MeOH); IR (KBr; ν, cm^{-1}) 3421, 3090, 1772, 1655 sh, 1623, 1464, 1385, 1284, 1217, 1013; EI-MS, m/z (%) 154 ($[M^{\cdot+}]$, 14), 136 (10), 126 (35), 110 (33), 97 (25), 84 (32), 82 (22), 71 (12), 69 (17), 57 (100), 55 (52); ^{1}H NMR (CD_3COCD_3, TMS) δ, (J, Hz) 2.90 sl (OH), 4.367, dd (17.2, 4.0, H5a), 4.643, dd (17.2, 2.8, H5b), 6.02-6.10, m (H1, H4, and H7); ^{13}C NMR (CD_3COCD_3) δ, 59.6 (C5), 89.3 (C1), 108.9 (C4), 110.6 (C7), 147.2 (C2), 152.8 (C3), 169.5 (C8).

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Registry No. 1, 129240-51-3; **2**, 129311-85-9; patuline, 149-29-1.

Supplementary Material Available: Tables of fractional coordinates of the non-hydrogen atoms, fractional coordinates of the H atoms, anisotropic thermal parameters, bond lengths, bond angles, and torsion angles of molecules A, **1**, and B, **2** (8 pages); list of the observed and calculated structure factors (5 pages). Ordering information is given on any current masthead page.

Single Transition State in the Transfer of a Neutral Phosphoryl Group between Phenoxide Ion Nucleophiles in Aqueous Solution

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Received January 22, 1990

Abstract: The second-order rate constants (k_{ArO}) for reaction of substituted phenoxide ions with 4-nitrophenyl diphenyl phosphate obey a linear equation over a range of 18 substituents with pK_{ArOH} values spanning the pK_a of the leaving 4-nitrophenolate ion: $\log k_{ArO} = 0.53pK_{ArOH} - 6.6$. The linear plot is consistent with a mechanism involving a single transition state or a two-step process with a very reactive intermediate with two almost identical transition states for its formation and breakdown; the value of the exponent (0.53) is also not consistent with a regular stepwise process with a discrete intermediate. The symmetrical reaction of 4-nitrophenolate ion with the 4-nitrophenyl ester is slightly imbalanced whereby bond formation does not keep up with bond fission in the transition state; the transition state, therefore, has some phosphorylium ion character. Transfer of the diethylphosphoryl group between weakly basic oxyanion nucleophiles is probably a concerted process with a transition state with more of the character of the pentacoordinate intermediate than it has in the corresponding diphenylphosphoryl group transfer.

Introduction

Reaction of nucleophiles with neutral phosphoryl species has long been considered to involve pentacoordinate intermediates,[1] and the existence of pentacoordinate oxyphosphoranes[2] lends credence to this belief. This and other laboratories have provided substantial evidence for concerted processes in transfer reactions of *general* acyl groups between nucleophiles.[3-5] A concerted

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