Communications to the Editor

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STABLE CONFORMATION OF 2,6-CIS-DISUBSTITUTED 1-ACYL-1,2,3,6-TETRAHYDROPYRIDINES AND STEREOSELECTIVE FORMATION OF PALUSTRINE SIDE CHAIN

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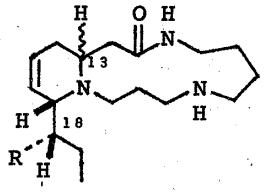
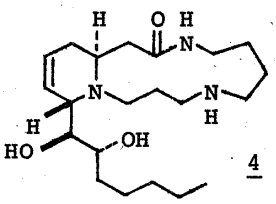
The 1-acyl-2,6-*cis*-disubstituted 1,2,3,6-tetrahydropyridine derivatives (5a-5d) were found to possess the structure of 5-A as a stable conformer. This knowledge was applied to a stereo-controlled formation of the side chain of palustrine (1) by causing an aldehyde (8) to react with Et_2CuLi. A chelated intermediate (8-C) may play an important role in the preferential production of the desired compound (9).

KEYWORDS——conformational analysis; 2,6-*cis*-disubstituted 1-acyl-1,2,3,6-tetrahydropyridine; $A^{1,3}$ strain; palustrine synthesis; metal chelate intermediate

In a recent communication,[1] we reported the stereoselective syntheses of (±)-18-deoxypalustrine (2) and its 13-epimer (3) for comparison with a minor alkaloid P_3, isolated from *Equisetum palustre* L.,[2] and established a synthetic route to a tetrahydropyridine molecule connected with a thirteen-member lactam ring, which is common to the structures of palustrine (1)[3] and cannabisativine (4).[4] Synthesizing the latter two alkaloids requires a device for the stereo-controlled introduction of hydroxyl groups into the alkyl side chains. In this report, we wish to describe a solution to this problem using a knowledge of conformational analysis of key compounds (5), obtained by our $SnCl_2$-mediated reaction of *endo*-peroxides derived from dihydropyridine derivatives.[5]



1 13β-H, R=OH
2 13β-H, R=H
3 13α-H, R=H



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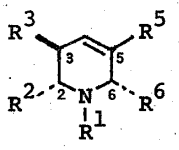

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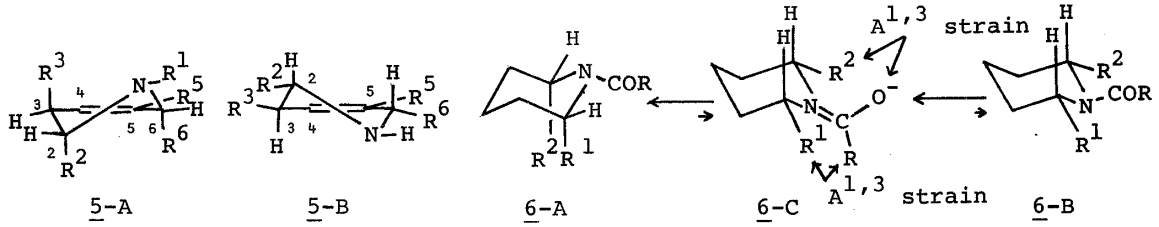
From the accumulated data, we selected compounds having an *N*-benzoyl or *N*-alkoxycarbonyl group (5a-5d) together with an NH derivative (5e) and summarized the coupling constant values of their ^1H NMR spectra in Table I. Two significant facts can be immediately recognized. (i) Judging from the similarity of the corresponding $J_{x,y}$ values, *N*-acyl derivatives (5a-5d) exist in the same conformer, irrespective of size or character of the substituents (R^2-R^6). (ii) Coupling constants between H-2 and H-3 of 5a-5d are observed in the range of 0—1.5 Hz and coincide well with the expected values when it is assumed that *N*-acyl compounds (5a-5d) possess the conformational structure of 5-A, where substituents at C-2,

Table I. ^{1}H NMR Coupling Constant of the Compounds (5)

	R^1	R^2	R^3	R^5	R^6	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$
5a	COPh	CH_2OCOPh	OAc	CN	OMe	1	1	5.5	–	1	–
5b	COOMe	Me	OAc	H	CH_2COPh	1.5	0	5.5	10	0	3
5c	Cbz	CH_2OAc	$OSiMe_2(t\text{-Bu})$	H	$CH_2CH(OEt)_2$	0	0	5	10	2	3
5d	Cbz	$CH{=}CH_2$	OCH_2Ph	H	$CH_2CH(OEt)_2$	1.5	0	5.5	10	1.5	3
5e	H	Pr	OH	H	$CH_2CH(OMe)_2$	8.5	0	3	†	†	†

† Coupling constant could not be determined.



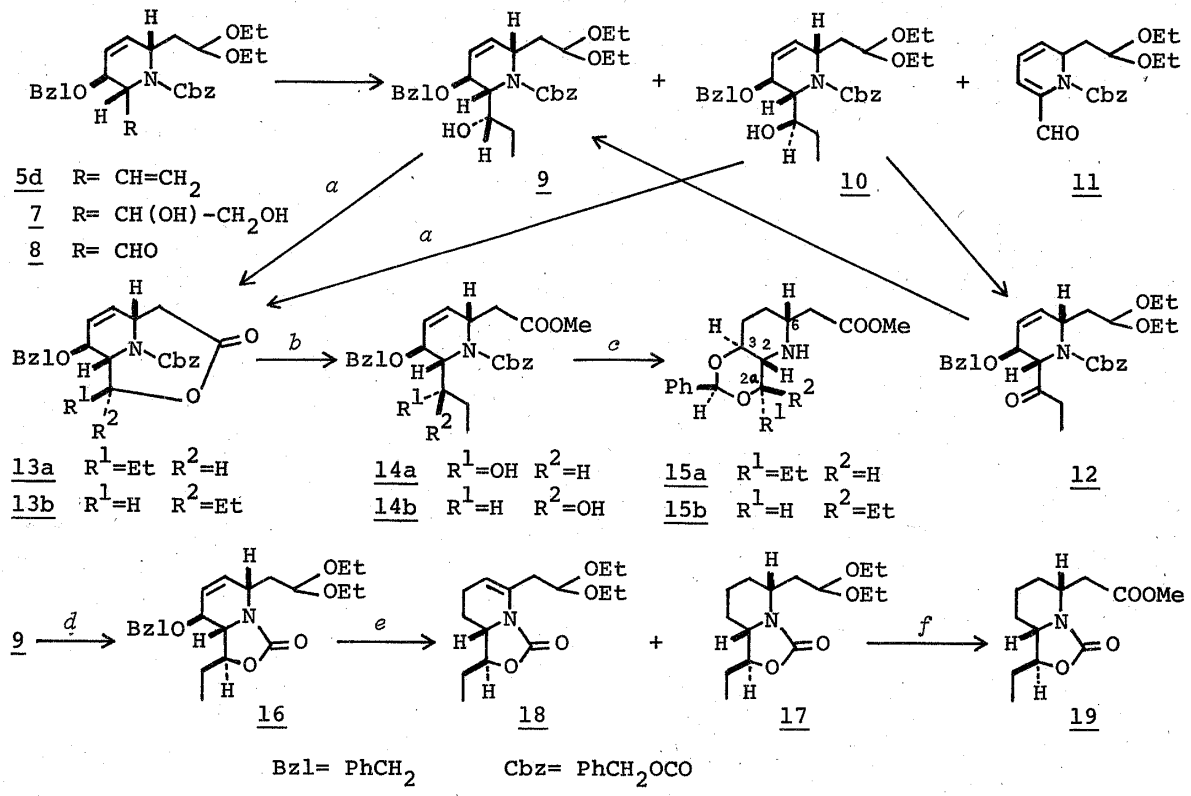
5-A 5-B 6-A 6-C 6-B

C-3, and C-6 are situated in the pseudoaxial orientation. On the other hand, the completely different $J_{2,3}$ value of 5e (8.5 Hz) suggests that the NH compound (5e) takes another conformation with H-2 and H-3 in the *trans* pseudodiaxial relationship.

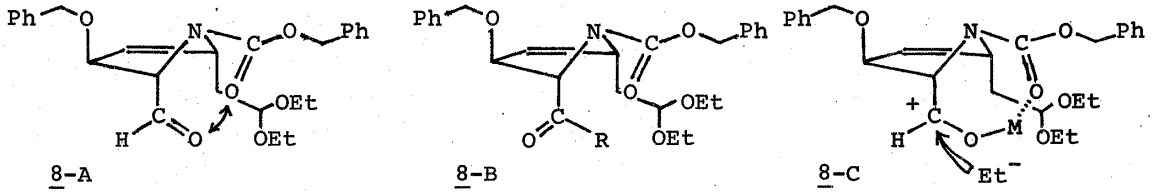
These facts correspond to the well-known observation[5b,6] that 1-acyl-2- or 2,6-substituted piperidine derivatives exist preferentially in the form of 6-A, whose stability is explained by relief of the $A^{1,3}$ strain[7] (6-C) originating from repulsion between equatorial substituents at α-position and an enolate form of the acyl group. This strian may also apply to our derivatives (5a-5d) as the main factor causing the conformer (5-A) to be predominant.

In a previous communication,[5d] we reported regioselective α-glycol formation only at the vinyl double bond of 5d with OsO_4 or $KMnO_4$, followed by cleavage with $NaIO_4$ to give an aldehyde derivative (8) in a good yield. This regioselectivity was only attained with bulky *O*-substituents such as $PhCH_2$ and *tert*-$BuMe_2Si$ groups and is now reasonably manifested by the conformer (5-A) in which the big substituents R^3 and R^6 cover both sides of the double bond in the piperidine ring from attack of the oxidizing reagents.

In order to construct the side chain of palustrine (1), the reaction of Et^- with the above-mentioned aldehyde (8) was investigated extensively (Table II), and both EtMgBr and EtLi were found to furnish in poor yield the product (10) with the undesired configuration of the hydroxyl group, accompanied by formation of an unstable compound (11). This result is clearly explained by assuming that the dipole-dipole repulsion (8-A) between the two carbonyls in 8 caused the aldehyde function to occupy mostly the rotationally isomeric position (8-B, R=H) and the Et^- approached the carbonyl from the unhindered front side. This consideration at once led us to attempt fixation of the aldehyde rotation at the stage of 8-A by insertion of a chelating metal with size suitable to fit into the two carbonyls. A good result was obtained by application of Et_2CuLi. The predominant formation of 9 is explained by the attack of the Et^- at the front side of a metal-chelated intermediate (8-C, M=Cu). The copper reagent did not behave as a base, which abstracted the proton to



a: i) 10% HCl-DME (1:2), r.t.; ii) $(F_3CCO)_2O$, DMSO, Et_3N, CH_2Cl_2, -75°C→r.t. *b*: 0.5% KOH-MeOH, 0°C. 9→14a: 71%. 10→14b: 73%. *c*: i) H_2, 10% Pd-C, HCl-MeOH, r.t.; ii) PhCHO, $ZnCl_2$, r.t. 14a→15a: 79%. 14b→15b: 81%. *d*: 5% KOH-MeOH, r.t., 90%. *e*: i) Na, liq. NH_3; ii) TsCl, Py, r.t.; iii) H_2, Raney Ni (W-2), MeOH, r.t., 17: 44%, 18, 9%. *f*: i) 10% HCl-DME (1:1), r.t.; ii) Ag_2O, EtOH-H_2O; iii) CH_2N_2, Et_2O-MeOH, 83%.



8-A 8-B 8-C

Table II. Formation of 9, 10, and 11 from 8

Reagent	Yield (%) calculated from 7		
	9	10	11
EtMgBr	¶	26	61
EtLi	8	26	¶
Et_2CuLi	62	18	0
$EtCu(Bu_3P)_n$ §	30	6	0
EtMgBr-CuI-Me_2S	47	25	0

¶ Detected on a TLC plate.

§ M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, Tetrahedron Lett., 21, 1247 (1980).

afford 11 from the carbon atom adjacent to both the aldehyde and urethane groups.

The unwanted compound (10) was oxidized with $(F_3CCO)_2O$-DMSO-Et_3N[8] (-60→0°C) (83%) to the ketone derivative (12), which was reduced with $LiBH_4$ in MeOH at 0°C to afford 9 in 97% yield, accompanied by recovery of 10 in 2% yield. Here, the rotational isomer (8-B, R=Et) played an important role against the hydride addition. In this way, preparation of the desired compound (9) was achieved in a completely stereoselective manner.

Structures of 9 and 10 were determined by respective transformation into 15a [^{1}H NMR (C_6D_6) δ: 0.96 (t, J=7 Hz, $CH_2\underline{CH_3}$), 1.33 (s, exchangeable with D_2O, NH), 2.13 (d, J=6 Hz, $\underline{CH_2}COOMe$), 2.93 (dd, J=9.5, 5.5 Hz, H-2), 3.36 (s, $COO\underline{CH_3}$), 3.51 (ddd, J=9.5, 9.5, 4 Hz, H-3), 3.86 (ddd, J=11.5, 5.5, 4 Hz, H-2a), 5.70 (s, -O-$\underline{CH}$Ph-O-)] with $J_{2,2a}$=5.5 Hz and 15b [^{1}H NMR (C_6D_6) δ: 1.03 (t, J=7.5 Hz, $CH_2\underline{CH_3}$), 1.86 (s, exchangeable with D_2O, NH), 2.42 (dd, J=9, 9 Hz, H-2), 3.36 (s, $COO\underline{CH_3}$), 5.56 (s, -O-$\underline{CH}$Ph-O-)] with $J_{2,2a}$=9 Hz, whose ^{1}H NMR spectra suggest the configuration of the Et group as shown. Final proof was obtained by conversion of 9 into a cyclic carbamate (19), which was identical with the authentic sample[9] prepared by Weinreb and collaborators from Eugster's synthetic methyl dihydropalustramate.[10]

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