NEOPULCHELLIN CONFORMATION

Seiichi Inayama,* Kenzo Harimaya, Hitoshi Hori, Takeshi Kawamata,
Tamiko Ohkura, Hikaru Nakamura,† and Yoichi Iitaka†
Pharmaceutical Institute, School of Medicine, Keio University, 35
Shinanomachi, Shinjuku-ku, Tokyo 160, and Faculty of Pharmaceutical
Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113,†
Japan

Abstract――Neopulchellin (1) was found to show that the cycloheptane
ring fused to the cis butyrolactone adopts a boat conformation both in
solid and in solution, in contrast with the half-chair form in the trans-
lactone isomer, pulchellin (3), on the basis of X-ray diffraction of 1
and comparison of 400 MHz [1]H-nmr and cd spectra of 1 and 3.

In the course of our medico-chemical studies on pseudoguaianolides in Gaillardia
pulchella, we reported the isolation and structural determination of pulchellin
(3) as the dominant principle of this plant.[1] X-ray analysis of 11,13-dibromo-
pulchellin revealed that the cycloheptane ring takes a half-chair conformation in
conjunction to the envelope of the cyclopentane and butyrolactone rings.[2] On the
other hand, neopulchellin (1), a C(8)-epimer of 3, was isolated as a minor
constituent and its stereostructure was also elucidated.[3] However, concerning the
conformation of its cycloheptane, it has remained in question whether a chair or
boat is favored when in solid or in solution, respectively, and vice versa. Since
we were encouraged by the recent structural elucidation of the other minor
constituents, pulchelloid A and B (i.e. 1-angeroyl- and 1-isovaleroyl-6β,9β-
dihydroxypulchellin) using the 400 MHz [1]H-nmr spectra,[4] it was considered that
this conformation problem might solve if every proton in the less substituted
analogue (1) in comparison with those pseudoguaianolides could be completely
assigned by the same manner as above. We now wish to report our findings that the
cycloheptane ring in 1 takes a boat conformation both in solution and in solid
state, which was estsblished by means of the proton nmr and cd spectroscopy as

Table 1. 400 MHz [1]H-nmr chemical shifts (multiplicities) of neopulchellin (1),
diacetylneopulchellin (2), pulchellin (3) and diacetylpulchellin (4)[a]

H	1[b]	3[b]	2[c]	4[c]
1	1.76 (dd)	1.96 (dd)	1.68 (dd)	2.01 (dd)
2	4.05 (dddd)	4.20 (dddd)	4.73 (ddd)	4.89 (ddd)
3α	1.53 (dd)	1.64 (dd)	1.50 (dd)	1.56 (dd)
3β	2.66 (ddd)	2.50 (ddd)	2.61 (ddd)	2.47 (ddd)
4	3.68 (dd)	3.69 (dd)	4.54 (d)	4.63 (d)
6α	2.12 (dd)	2.86 (dd)	1.37 (dd)	1.95 (dd)
6β	1.50 (dd)	1.14 (dd)	0.95 (dd)	0.54 (dd)
7	3.52 (ddddd)	2.84 (ddddd)	2.88 (ddddd)	2.31 (ddddd)
8	4.80 (ddd)	4.24 (ddd)	4.13 (ddd)	3.35 (ddd)
9α	1.83 (ddd)	1.43 (ddd)	1.45 (ddd)	0.93 (ddd)
9β	2.04 (ddd)	2.39 (ddd)	1.51 (ddd)	1.87 (ddd)
10	1.96 (dddq)	1.94 (dddq)	1.30 (dddq)	1.20 (dddq)
13 a	6.25 (d)	6.17 (d)	6.18 (d)	6.07 (d)
13 b	5.63 (d)	5.48 (d)	4.95 (d)	4.86 (d)
14	1.26 (d)	1.24 (d)	0.78 (d)	0.75 (d)
15	0.82 (s)	0.87 (s)	0.25 (s)	0.26 (s)
2-OH	1.71 (d)	1.81 (d)	-OAc {1.60 (s)	-OAc {1.63 (s)
4-OH	1.86 (d)	2.00 (d)	1.62 (s)	1.67 (s)

a, δ (ppm).   b, in $CDCl_3$.   c, in C_6D_6

well as X-ray crystallography, in a striking contrast to the half-chair form of
the corresponding ring in 3. However, separation of 1 from 3 was effected only by
a laborious task such as repeated liquid chromatography of the mixed acetates of
both isomers following by deacetylation.[3] Highly efficient isolation of 1 from
the so-called pulchellin mixture (1:3/3:5) was first achieved in good yield with
high-performance liquid chromatography (μ-Porasil Semi Prep, $CHCl_3$-EtOH/9:1, 254
nm). The chemical shifts and multiplicities for all protons in the 400 MHz [1]H-nmr
spectra of 1 and its acetate (2) are shown in Table 1. For example, in the case
of 2, the multiple signal at δ 2.88 was assigned to H-7 by irradiation of each
doublet signal of H-13a (δ 6.18) and H-13b (δ 4.95). When the H-7 signal was
irradiated, not only H-13a and H-13b doublets changed to singlets, but also a H-8
doublet of double doublets (δ 4.13) to a double doublet. The coupling constants
of H-13a (2.4 Hz) and H-13b (2.2 Hz) are characteristic of the cis-fused α-
methylene-γ-butyrolactone ring as assigned previously.[3,5] Other proton signals
(H-1, H-2, H-3β, H-4, H-6α, H-6β, H-10) were also assigned by decoupling ex-
periments. Whereas H-3α, H-9α, and H-9β signals were not easily assigned due to
their complex overlapping, entirely clear separation of these proton signals was
achieved by adding the shift reagent Eu(fod)$_3$. The coupling constants observed

for all signals of 2 are thus defined. Fig. 1 shows the corresponding J-values in 1 for a comparison. As a result of these experiments, the chemical shifts and multiplicities for each proton of 2 were assigned as shown in Table 1. A comparison of the observed J-values such as $J_{6\alpha,7}$ (3.8 Hz), $J_{6\beta,7}$ (13.5 Hz), $J_{7,8}$ (7.8 Hz), $J_{8,9\alpha}$ (4.0 Hz), $J_{8,9\beta}$ (11.9 Hz), $J_{9\alpha,10}$ (1.6 Hz), $J_{9\beta,10}$ (6.5 Hz) and $J_{10,1}$ (11.6 Hz) with those deduced from Dreiding models led to the conclusion that the cycloheptane of 2 would take a boat form as the more favorable conformation. It is impossible to explain the proper conformation reasonably based on the above-mentioned [1]H-nmr data if the cycloheptane of 1 or 2 adopts a chair form. The coupling constants observed in 1 for H-8/H-9α (3.6 Hz), H-8/H-9β (12.3 Hz), H-9α/H-10 (1.1 Hz), and H-9β/H-10 (6.5 Hz), except for H-6, H-7 and H-10, exhibit a sharp contrast with those of 3 having a half-chair conformation as described later. On the other hand, from observed coupling constants such as $J_{1,10}$ (11.6 Hz), $J_{2,3\alpha}$ (2.8 Hz), $J_{2,3\beta}$ (9.1 Hz), $J_{3\alpha,4}$ (0), $J_{3\beta,4}$ (5.0 Hz), it is confirmed that the cyclopentane ring taking in an envelope form with the flap at C(5) is trans-fused to the cycloheptane ring as stated previously.[3] This fact is further supported by the observation of nuclear Overhauser enhancement (8%) between the C(10)-methine proton and the angular C(5)-methyl protons; that is, no NOE enhancement would be expected if these two rings are cis-fused (1βH/15βCH$_3$). A strong negative cd Cotton effect of 1 ([θ]$_{255}$ -56800) shown at 0°C to 27°C unchanged even at 60°C. The cycloheptane ring fused to the cis-butyrolactone ring[6] is therefore considered to be rigidly fixed in a boat conformation in solution as in a solid state as described below. In contrast, 3 displays the opposite sign of Cotton effect ([θ]$_{259}$ +11900), indicating the trans-butyrolactone ring[6] fused to the corresponding middle ring in a half-chair conformation.[2]
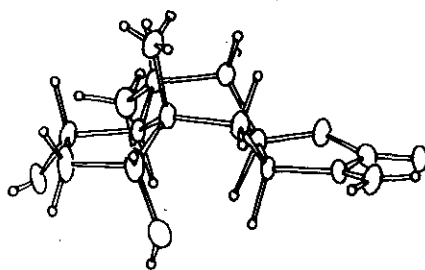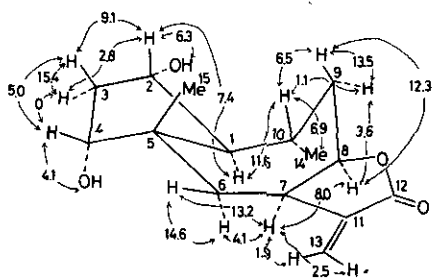

Fig. 1. [1]H-nmr J-values of neopulchellin (1). Fig. 2. Perspective view of (1).

To confirm the conformation in solution of this <u>trans</u>-<u>cis</u> pseudoguaianolide, X-ray analysis of neopulchellin itself was performed to establish its crystal structure. A single crystal of <u>1</u> (<u>ca</u>. 0.1 x 0.2 x 0.11 mm) obtained by recrystallization from Et_2O-AcOEt afforded crystal data as follows: $C_{15}H_{22}O_4$, MW 266, Monoclinic, Space group $P2_1$, z= 2, <u>a</u>= 8.308(5), <u>b</u>= 10.494(5), <u>c</u>= 7.921(4) Å, β= 103.57(5)°, U= 671.3 Å³ and Dc= 1.318 g·cm⁻¹. The cell dimension and intensity data were collected on a four-circle diffractometer using graphite monochromated CuKα radiation. The crystal structure was solved by the direct method using MULTAN.[7] Refinement was carried out by the least-squares method with block-diagonal matrix approximations. Twenty two hydrogen atoms were found on the difference electron density map and were included in the refinement assuming as isotropic thermal vibration. The final R value for 921 reflections was 0.053.

As shown in Fig. 2, the cycloheptane ring of <u>1</u> takes a boat conformation, which is constructed by the central plane encompassing C(5)-C(6)-C(9)-C(10) and the wing planes consisting of C(6)-C(7)-C(8)-C(9) and C(5)-C(1)-C(10). Consequently, the cyclopentane ring for <u>3</u> and <u>1</u> is similarly fused in the C(5)-flap envelop form to the chair and boat cycloheptane ring, to which the <u>trans</u>- and <u>cis</u>-γ-butyrolactone ring is united in an almost flat shape, respectively. The dihedral angles in the solid state of <u>1</u> as shown in Table 2, which were obtained by the X-ray analysis, suggest the boat form cycloheptane. The cd Cotton effect for <u>1</u> was independent of changes in temperature as mentioned above. Therefore, it seems self-evident that the boat conformation of the cycloheptane ring in solution of <u>1</u> is rigidly fixed and entirely similar to that in the soled state. For further comparison, in the ¹H-nmr data for <u>3</u> and its acetate (4) (see Table 1), the coupling constants of $J_{7,13a}$ (3.3 Hz), $J_{7,13b}$ (3.3 Hz), and $J_{7,8}$ (9.1 Hz) attributed to the <u>trans</u>-fused α-methylene-γ-butyrolactone ring[1,4,5] is in a remarkable contrast to the corresponding part of <u>1</u> and <u>2</u>. It is of interest to note that $J_{8,9\alpha}$ (11.8 Hz), $J_{8,9\beta}$ (3.3 Hz), $J_{9\alpha,10}$ (11.6 Hz) and $J_{9\beta,10}$ (3.6 Hz), except almost the same J-values for H-6, H-7 and H-10, as observed in <u>1</u>, suggest a half-chair conformation of the

Table 2. Dihedral angles in solid in neopulchellin (1) based on the X-ray data

1,2	160.57°	3β,4	22.32°	8,9α	82.68°
1,10	173.48°	6α,7	44.19°	8,9β	160.10°
2,3α	142.68°	6β,7	172.16°	9α,10	76.92°
2,3β	10.60°	7,8	0.28°	9β,10	32.18°
3α,4	92.28°				

cycloheptane ring in solution, in agreement with that of 11,13-dibromopulchellin in the solid state.[3] Further studies on the relationship between the conformations and biological activities of neopulchellin derivatives are now in progress.

REFERENCES

1. M. Yanagita, S. Inayama, and T. Kawamata, Tetrahedron Lett., 1970, 131. References loc. cit.

2. T. Sekita, S. Inayama, and Y. Iitaka, Tetrahedron Lett., 1970, 135; idem., Acta Crystallogr., 1970, B27, 877.

3. M. Yanagita, S. Inayama, and T. Kawamata, Tetrahedron Lett., 1970, 3007.

4. S. Inayama, K. Harimaya, T. Ohkura, and T. Kawamata, Heterocycles, 1982, 17, 219.

5. Z. Samek, Tetrahedron Lett., 1970, 671.

6. W. Stöcklin, T. G. Waddell, and T. A. Geissman, Tetrahedron, 1970, 26, 2397.

7. P. Main, M. M. Woolfson, and G. Germain, Acta Crystallogr., 1971, A27, 368.

The fractional atomic cordinates for neopulchellin ($\underset{\sim}{1}$)

	ATOM	F	MUL	X	Y	Z	B1:
	TABLE OF COORDINATES FOR ATOMS NOT REFINED						
1	C1	1	1.0	0.24249	0.71520	0.77805	
2	C2	1	1.0	0.21759	0.83006	0.89195	
3	C3	1	1.0	0.14507	0.77483	1.03645	
4	C4	1	1.0	0.15219	0.62754	1.02056	
5	C5	1	1.0	0.28094	0.60491	0.91516	
6	C6	1	1.0	0.27140	0.46871	0.83290	
7	C7	1	1.0	0.17294	0.45530	0.64433	
8	C8	1	1.0	0.23765	0.53363	0.50997	
9	C9	1	1.0	0.39799	0.60781	0.57543	
10	C10	1	1.0	0.36733	0.73469	0.66750	
11	C11	1	1.0	0.17557	0.31948	0.57883	
12	C12	1	1.0	0.22041	0.31972	0.41203	
13	C13	1	1.0	0.15823	0.21098	0.66259	
14	C14	1	1.0	0.31340	0.84005	0.53127	
15	C15	1	1.0	0.45423	0.61940	1.03639	
16	O1	3	1.0	0.27205	0.44009	0.38086	
17	O2	3	1.0	0.10992	0.92304	0.79163	
18	O3	3	1.0	-0.00864	0.57501	0.94258	
19	O4	3	1.0	0.22345	0.23488	0.31250	
20	H(C1)	2	1.0	0.11814	0.69644	0.68514	
21	H(C2)	2	1.0	0.34846	0.86247	0.94166	
22	H(C3)	2	1.0	0.02720	0.79648	1.02358	
23	H'(C3)	2	1.0	0.21618	0.78727	1.18178	
24	H(C4)	2	1.0	0.17073	0.59092	1.13474	
25	H(C6)	2	1.0	0.39422	0.44130	0.84163	
26	H'(C6)	2	1.0	0.22116	0.42766	0.90922	
27	H(C7)	2	1.0	0.03583	0.47312	0.64840	
28	H(C8)	2	1.0	0.10588	0.59671	0.44251	
29	H(C9)	2	1.0	0.49293	0.56195	0.66492	
30	H'(C9)	2	1.0	0.45454	0.62881	0.47400	
31	H(C10)	2	1.0	0.50575	0.74410	0.74251	
32	H(C13)	2	1.0	0.12751	0.20835	0.79637	
33	H'(C13)	2	1.0	0.17495	0.13723	0.60165	
34	H(C14)	2	1.0	0.38723	0.84332	0.45716	
35	H'(C14)	2	1.0	0.18959	0.82803	0.45833	
36	H"(C14)	2	1.0	0.32261	0.91620	0.62118	
37	H(C15)	2	1.0	0.52643	0.61358	0.96716	
38	H'(C15)	2	1.0	0.44067	0.54541	1.14520	
39	H"(C15)	2	1.0	0.46673	0.70522	1.08959	
40	H(O2)	2	1.0	0.07707	0.95745	0.85436	
41	H(O3)	2	1.0	-0.08189	0.61055	0.86997	