

NEOPULCHELLIN CONFORMATION

Seiichi Inayama,* Kenzo Harimaya, Hitoshi Hori, Takeshi Kawamata,
 Tamiko Ohkura, Hikaru Nakamura,† and Yoichi Iitakat
 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 ¹H-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-dibromopulchellin 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-6 β ,9 β -dihydroxypulchellin) using the 400 MHz ¹H-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 established by means of the proton nmr and cd spectroscopy as

Table 1. 400 MHz ^1H -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)
3 α	1.53 (dd)	1.64 (dd)	1.50 (dd)	1.56 (dd)
3 β	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)
6 α	2.12 (dd)	2.86 (dd)	1.37 (dd)	1.95 (dd)
6 β	1.50 (dd)	1.14 (dd)	0.95 (dd)	0.54 (dd)
7	3.52 (dddd)	2.84 (dddd)	2.88 (dddd)	2.31 (dddd)
8	4.80 (ddd)	4.24 (ddd)	4.13 (ddd)	3.35 (ddd)
9 α	1.83 (ddd)	1.43 (ddd)	1.45 (ddd)	0.93 (ddd)
9 β	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)	-OAc{ 1.62 (s)	-OAc{ 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 ^1H -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-3 β , H-4, H-6 α , H-6 β , H-10) were also assigned by decoupling experiments. Whereas H-3 α , H-9 α , and H-9 β signals were not easily assigned due to their complex overlapping, entirely clear separation of these proton signals was achieved by adding the shift reagent $\text{Eu}(\text{fod})_3$. 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 ^1H -nmr data if the cycloheptane of **1** or **2** adopts a chair form. The coupling constants observed in **1** for H-8/H-9 α (3.6 Hz), H-8/H-9 β (12.3 Hz), H-9 α /H-10 (1.1 Hz), and H-9 β /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 ($1\beta\text{H}/15\beta\text{CH}_3$). A strong negative cd Cotton effect of **1** ($[\theta]_{255} -56800$) shown at 0°C to 27°C unchanged even at 60°C. The cycloheptane ring fused to the cis-butyrolactone ring⁶ 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 ($[\theta]_{259} +11900$), indicating the trans-butyrolactone ring⁶ fused to the corresponding middle ring in a half-chair conformation.²

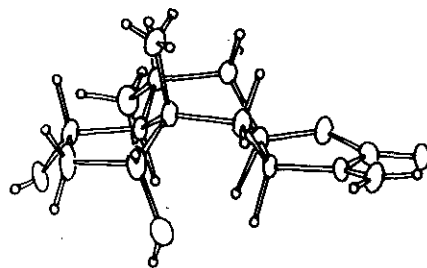
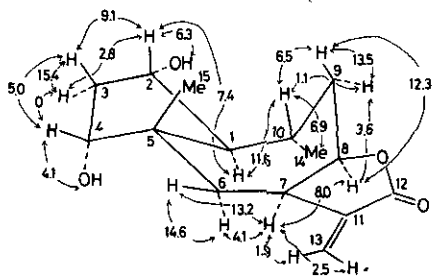


Fig. 1. ^1H -nmr J-values of neopulchellin (**1**). Fig. 2. Perspective view of (**1**).

To confirm the conformation in solution of this trans-cis pseudoguaianolide, X-ray analysis of neopulchellin itself was performed to establish its crystal structure. A single crystal of 1 (ca. 0.1 x 0.2 x 0.11 mm) obtained by recrystallization from Et₂O-AcOEt afforded crystal data as follows: C₁₅H₂₂O₄, MW 266, Monoclinic, Space group P2₁, z = 2, a = 8.308(5), b = 10.494(5), c = 7.921(4) Å, β = 103.57(5)°, U = 671.3 Å³ and D_c = 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 1 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 3 and 1 is similarly fused in the C(5)-flap envelop form to the chair and boat cycloheptane ring, to which the trans- and cis-γ-butyrolactone ring is united in an almost flat shape, respectively. The dihedral angles in the solid state of 1 as shown in Table 2, which were obtained by the X-ray analysis, suggest the boat form cycloheptane. The cd Cotton effect for 1 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 1 is rigidly fixed and entirely similar to that in the solid state. For further comparison, in the ¹H-nmr data for 3 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 trans-fused α-methylene-γ-butyrolactone ring^{1,4,5} is in a remarkable contrast to the corresponding part of 1 and 2. It is of interest to note that J_{8,9α} (11.8 Hz), J_{8,9β} (3.3 Hz), J_{9α,10} (11.6 Hz) and J_{9β,10} (3.6 Hz), except almost the same J-values for H-6, H-7 and H-10, as observed in 1, 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.

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The fractional atomic coordinates for neopulchellin (I)

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	0.21018	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	0.18459	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

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