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NEOPULCHELLIDINE AND NEOPULCHELLIN

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It has been cited in the previous communications that pulchellidine(Ia)(1, 2, 3) was accompanied by a new minor sesquiterpene alkaloid, neopulchellidine(I), and that a new lactone isomer of pulchellin(IIa)(2, 3, 4), neopulchellin(II), was isolated pure from the Japanese cultivation(2). We now wish to report the stereostructure determination of I and II. The stereochemical relationship of I and II with Ia and IIa(2, 3), respectively, are also disclosed in the present paper[*2].

Diacetylneopulchellin was separated gas chromatographically[*3] pure from diacetylpulchellin by repeated combination of recrystallization and column chromatography as described in the preceeding paper(2). Diacetylneopulchellin: $C_{19}H_{26}O_6$[*4] ; mp 151.5-152.5° ; $(\alpha)_D^{20°}$ +26.0°(c, 1.73)[*4] ; UV λ 213 (7684) ; IR[*4] ν 1761, 1658($\Delta^{\alpha,\beta}$-γ-lactone), 1733, 1251; NMR δ 5.00 c (H_2), 4.74 d,5 (H_4), 4.80 c (H_8), 6.24 d,2 & 5.48 d,2 ($2xH_{13}$), 1.02 d,7 ($3xH_{14}$), 0.95 s ($3xH_{15}$). Hydrolysis with 5% KOH-Dioxane led to good recovery of II (Fig. 1), which reverted to the starting acetate like in the case of IIa(2). Neopulchellin(II): $C_{15}H_{22}O_4$; mp 166.5-167.5° ; $(\alpha)_D^{25°}$ +43.0°(c, 1.01) ; λ 213 (9865) ; ν 3548, 3482 (hydroxyl), 1754, 1659 ($\Delta^{\alpha,\beta}$-γ-lactone) ; δ 4.00 c (H_2), 3.68 d,5 (H_4), 4.70 c (H_8), 6.23 d,3 & 5.66 d,3 ($2xH_{13}$), 1.25 d,5 ($3xH_{14}$), 0.81 s ($3xH_{15}$). Sulfite: $C_{15}H_{20}O_5S$; mp 165.5-167.5°(d.). It is interesting that the piperidine adduct of II, similarly made as that of IIa(1, 2), was now found to be identical with the authentic sample of I(1) in all respects (Fig. 2). Neopulchellidine(I): $C_{20}H_{33}O_4N$; mp 131-

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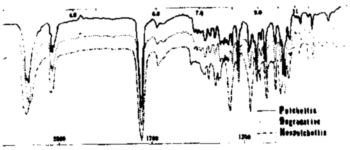
[*2] Presented in the 13th symposium on Chemistry of Natural Products of Japan held in Sapporo, Sep. 25-27, 1969; paper abstracts p.257-264.

[*3] Silicon OV-17 1.5% on 80/100" Chromosorb-AW; column temp. 225° and Sample 300°.

[*4] Elementary analyses, rotations($CHCl_3$), TLC and absorption spectra were run and recorded in the usual manner as described in the preceeding paper (1, 2).



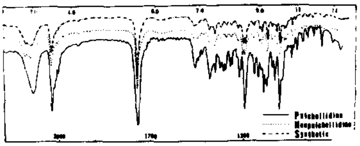
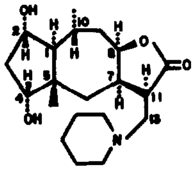


Fig. 1. The IR-spectra of neopulchellin(II) and pulchellin(IIa).
Fig. 2. The IR-spectra of neopulchellidine(I) and pulchellidine(Ia).

134° ; $(\alpha)_D^{21°}$ -13.0°(c, 1.0), ν 3384, 3512, 1774 ; δ 4.00 c (H_2), 3.58 d,6 (H_4), 4.80 c (H_8), 1.25 d,6 ($3xH_{14}$), 0.82 s ($3xH_{15}$) ; TLC 0.57 ; GLC for TMS derivative 7.54 min [cf. 8.20 min for TMS-Ia]. The IR-spectra of II and IIa are similar with each other, but significant differences are present in their finger print regions (Fig. 1) as well as in those of I and Ia (Fig. 2).

From the negative ΔM_D of II(-23.4) with its acetate, cis-cyclopentane-2,4-diol(cyclic sulfite v.s. and cyclopentenone formation v.i.) in II should have the same α configuration as C_2-OH of IIa(2, 3). On the other hand, the NMR signal of C_4-H appeared as doublet(J≃5-6 Hz) centered at 3.68(II), 4.74(II-acetate), 3.58 (I), 4.66(I-acetate) and 3.89(IV) v.i., suggesting β of C_4-H to be cis to C_5-βCH_3 as described in IIa(2, 3).



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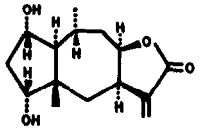
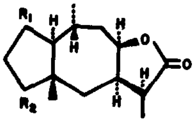


II



	R_1	R_2
III :	..OH	..OH
IV :	=O	..OH
V :	VI(Δ^3)	
VI :	=O	H_2

Catalytic hydrogenation or $NaBH_4$ reduction of II under same conditions as in IIa(2) gave almost equal amounts of the epimeric mixture(1:1) of dihydro derivative of II checked with GLC*3. Attempted epimerization of the epimeric mixture mentioned above at C_{11}(ca. 1:1) with 1%-NaOMe(100°, 2hr, seald tube) afforded an equillibration mixture(6:1) of the dihydroneopulchellins [GLC 19.5 min cf. 22.3 min for IIIa], in which the C_{11}-βCH_3 should be predominant. It is note of interest that the hydrogenation and chemical reduction of II shows the different mode on stereoselectivity from those of IIa(2). This suggests that C_8-ether bond of the lactone of II should take quasi axial position, in contrast with quasi equatorial configuration of the corresponding group of IIa(2, 3). Dihydroneopulchellin(III): $C_{15}H_{24}O_4$; mp 185-188°(prisms); $(\alpha)_D^{20°}$ +50.0°(c, 1.08; 50%-MeOH) and -16.9°(c, 1.04; 50%-MeOH) for the hydroxy acid salt(ΔM_D +47.7°); ν 3498, 3418, 1759; δ 4.00 c (H_2), 3.59 d,6 (H_4), 4.80 c (H_8), 0.82 s ($3xH_{15}$), 1.26 d,7 ($3xH_{14}$), 1.33 d,7 (1.32 in py.)($3xH_{13}$). Diacetate: $C_{19}H_{28}O_6$; mp 164-166°; $(\alpha)_D^{25.5°}$ +52.0°(c, 0.77); ν 1771, 1739; δ 4.80 c (H_2), 4.69 d,6 (H_4), 4.80 c (H_8), 2.04 s & 2.08 s ($2xOCOC\underline{H}_3$), 0.95 s ($3xH_{15}$), 1.07 d,6.0 ($3xH_{14}$), 1.33 d,7.2 ($3xH_{13}$).

C_{11}-βCH_3 configuration in the dihydro derivative was deduced as in those of IIa(2) from little solvent shifts($\delta^{CDCl_3-C_5H_5N}$) (5) for III(+0.01), III-acetate (-0.03) and IV(+0.02) *v.i.* The more bulky C_{11}-$CH_2NC_5H_{10}$ grouping of I should be formed by stereoselective addition of piperidine to II, being probably indicative of thermodynamically more stable β configuration as α in Ia(2, 5).

C_8-αH configurations of I and II were established from the positive shift of molecular rotation of III with that of the corresponding hydroxy acid salt(ΔM_D +183.4°) [cf. +7.7° for III(1:1)], by application of the Hudson-lactone rule. Each sign of Cotton effects of II on cautious RD and CD determinations (MeOH) at about 230-280 mμ for the α-methylene-γ-lactone n→π* transition show negative [a -54.6 and $(\theta)_{250}$ -3003], respectively(cf. 7). These RD and CD data are clearly in sharp contrast with the case of IIIa and IIa(2), and also in accordance with difficulty of alkaline lactone fission(III is almost 6 times slower than IIIa). Hence the stereochemistry of γ-lactone junction with cycloheptane ring in II and III can be assigned as C_8-αH/C_7-αH(*cis*).

The upward shifts of C_{10}-methyl signals(0.17, 0.23, 0.19 and 0.11) were observed on structural changes from I, II, III and IV *v.i.* to I, II-, III-acetate and III, respectively. The C_{10}-methyl configurations in I and II should be then estimated same α as in Ia and IIa(2, 3), when they are in *trans*-bicyclo(5.3.0) decane ring fusion, which is proved the case as follows.

The hydroxyketone(IV), prepared from III by CrO_3/Py, was dehydrated by MsCl/Py to the cyclopentenone(V), which was in turn hydrogenated to the cyclopentanone (VI) as in IVa(2, 4). On comparison with the case of pulchellin series, it is noteworthy that stereochemistry at the ring junctions of IV has been hold even in the course of dehydration followed by hydrogenation to VI, both of which are of *trans*-fusions to be proved by RD data as previously(2). *trans*-Dehydrodihydroneopulchellin(IV): $C_{15}H_{22}O_4$; mp 190-192° ; $(\alpha)_D^{22°}$ +78.0°(c, 0.33) ; ν 3452, 1745, 1735 ; δ 3.96 d,4.8 (H_4), 4.81 q, 15.0, 7.5 (H_8), 0.88 s ($3xH_{15}$), 1.37 d,7.2 ($3xH_{14}$), 1.29 d,7.2 ($3xH_{13}$). The RD curve of the ketol(IV) displays a pronounced positive C.E. at 317-275 mμ in $CHCl_3$ solution(a +112.5), suggesting that the bicyclo(5.3.0)decane ring fusion must be *trans*(C_5-βCH_3/C_1-αH) being obeyed the Octant rule. Furthermore, the strong positive sign of C.E. of IV in HOAC solution hardly suffered any change in the sense (a +117.3 to +83.0) for 1.5 hr after addition of 1 drop of conc. HCl. It is of interest to note that *trans*-bicyclo(5.3.0)decane ring fusion of IV is much more stable than that of IVa with the same *trans* junction of the pseudoguaian-2-one system(cf. 2).

In conclusion, the full stereochemistry of neopulchellin and neopulchellidine has been thus established to be formulated as II and I, respectively.

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