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SESQUITERPENE LACTONES OF *GAILLARDIA PULCHELLA*

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Abstract—A Japanese cultivar of *Gaillardia pulchella* Foug. contained, in addition to the pseudoguaianolides, pulchellin(I) and neopulchellin(II), the guaianolide, gaillardin(III) apparently accompanied by its epimer neogaillardin(IV) and an unidentified basic principle different from pulchellidine(V) and neopulchellidine(VI). A possible biogenetic scheme for the sesquiterpene lactones including eudesmanolides, pulchellin-B, -C, -E and -F(VII) is proposed.

Sesquiterpene lactones of the title plant vary with the local of the collection. The first report on the coastal race native to North America showed that it produced a pseudoguaianolide, pulchellin(I).[1] A collection from the western USA was found to produce several eudesmanolides such as pulchellin-B(R=Ac, R′=H), -C(R=R′=H), -E(R=H, R′=Ac) and -F(R=angeroyl, R′=H)(VII)[2] and a guaianolide, gaillardin(III) was isolated from a Texas race.[3]

Our recent work on a collection of the coastal race was concerned with the isolation and structural elucidation of the novel sesquiterpene alkaloids, pulchellidine(V)[4,5] and neopulchellidine(VI),[6] which were related to pulchellin(I)[4,5] and neopulchellin (II),[6] respectively.

The present paper describes the isolation of gaillardin(III) apparently accompanied by its epimer(IV), together with pulchellin(I), neopulchellin(II) and an unidentified basic constituent from *Gaillardia pulchella* Foug. cultivated in Japan (Tenningiku). Thus I, II and III have been isolated from the same collection of *G. pulchella* for the first time. This supports the previously suggested[5c,7] biogenetic relationship between the guaianolide gaillardin(III) and the pseudoguaianolide pulchellin(I), and is expanded in Scheme 1 to include the eudesmanolides pulchellin-*B*–*D*(VII) and the pseudoguaianolide alkaloids pulchellidine(V) and neopulchellidine(VI).

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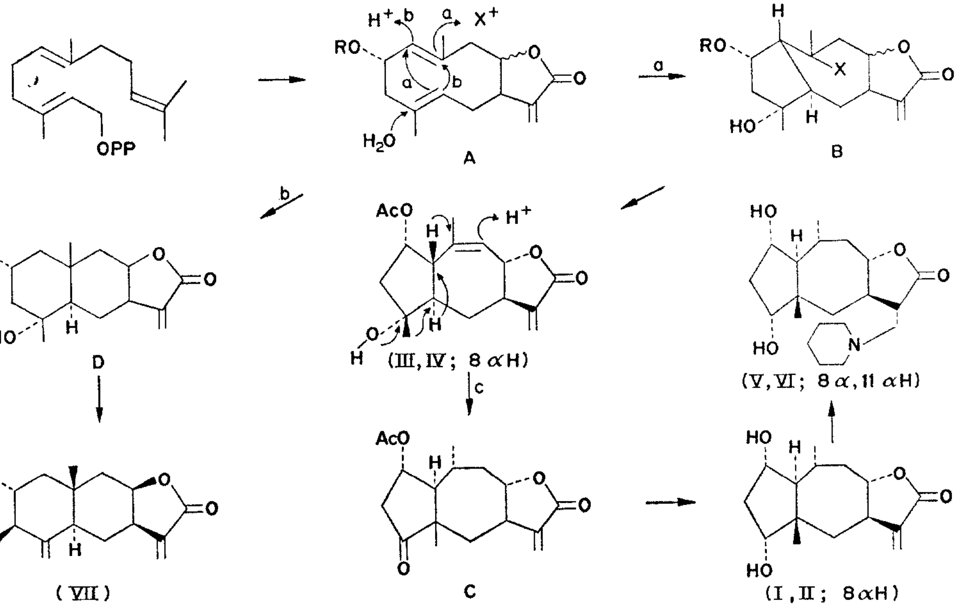

SCHEME 1. A POSSIBLE BIOGENETIC SCHEME FOR SESQUITERPENE LACTONES OF *Gaillardia pulchella*.

In accordance with the suggestion of Parker *et al.*,[8] anti-Markownikoff oriented, *trans*-anti-parallel cyclization of a hypothetical *cis*-$\Delta^{1,10}$-germacranolide(A), derived from a *trans*-farnesyl pyrophosphate progenitor, would lead to the guainolide, gaillardin(III) having $\Delta^{9,10}$-*trans*-bicyclo(5,3,0)-decane ring system *via* the intermediate (B) (route a) as shown in Scheme 1. It seems reasonable that the guaianolide(III) could be transformed to the pseudoguaianolide, pulchellin(I) throught the possible intermediate(C), as suggested[5c,7,8] by way of initial protonation, *trans*-anti-parallel consecutive 1,2-shifts of two hydrides and one methyl anion, and final deprotonation (route c). Subsequent biological hydrolysis and selective reduction in C would then result in formation of I. Several eudesmanolide principles such as pulchellin-B, -C, -E and -F(VII) found in a mountain race of the same plant[2] would be conceivably furnished from the precursor(A) *via* the possible intermediate(D). Acid-catalyzed Markownikoff oriented, *trans*-anti-parallel cyclization[7] of A (route b) followed by an adequate biological modification at C_3 and C_4 in D could be involved in the transformation of A to VII. Michael type addition of piperidine or its congener such as lysine to I and II accounts very well for the formation of V and VI.[4]

Gaillardin(III) was originally isolated only in the form of a hard-to-separate crystalline mixture of gaillardin(III) and an isomer assumed to be the *cis* lactone(IV) in a ratio of *ca.* 9:1. However, hydrogenation of the mixture followed by hydrolysis resulted in pure desacetyldihydrogaillardin,[3] indicating that the impurity(IV) had been eliminated. Similarly pulchellin(I) was previously assumed to be pure,[1] but later shown to be contaminated by a small amount of neopulchellin(II) in the ratio of about 5:1[4,6] and pulchellidine(V) was likewise difficult to separate from a contaminant, neopulchellidine(VI).[4]

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EXPERIMENTAL

Isolation of pulchellin(I), *neopulchellin*(II) *and gaillardin*(III) (partly with Mrs. T. Ohkura). The title plant cultivated at Shiki near Tokyo was harvested in September 1970. The chipped air dried whole plant (27·2 kg) was percolated with hot trichloroethylene and concentrated to a brownish gum (200 g). This was subjected to a column chromatography over neutral alumina (2·5 kg) in the usual manner. Elution with C_6H_6–$CHCl_3$ (3:1) afforded, after evaporation and crystallization from AcOEt–Et_2O, crude crystals, m.p. 174–80°, 2·129 g (0·00008 %, based on the dried material). The extensive recrystallizations from C_6H_6, C_6H_6–C_6H_{12}, EtOAc–C_6H_{12} and MeOH–C_6H_{12} combined with chromatography over charcoal, neutral alumina and silicic acid gave rise to colorless thin plates or elongated prisms, m.p. 189–90° or m.p. 193–4°, which represented an inseparable mixture of gaillardin(III) [m.p. 199–200° (vac)[3]] and neogaillardin(IV) giving a single compact spot on TLC. $C_{17}H_{22}O_5$ (Found: C, 66·29; H, 7·07; N, 0·00. Calcd: C, 66·65; H, 7·24%). IR spectra (KBr and $CHCl_3$) were essentially superimposable on those of gaillardin (III).* NMR signals ($CDCl_3$, 60 and 100 MHz) are in accord with the reported values,[3] but the spectrum determined at a higher concentration reveals a pair of peaks (rel. int. 1:11–13) (1·22*s*, 1·27*s* $C_{(4)}$–CH_3; 5·70 *d*, 3, 6·29 *d*, 3, 5·57 *d*, 3, 6·22 *d*, 3 $C_{(11)}{=}CH_2$ and 4·90 *m*, 4·50 *m* $C_{(8)}$–H), in which the minor peaks are characteristic for the neo-series of pseudoguaianolides.[4,6] $[\alpha]_D^{25}$ −0·90° (*c* 1·11, $CHCl_3$) [$[\alpha]_D^{30}$ −15° (*c* 1·08, $CHCl_3$)[3]]. GLC: R_t 1·65, 1·40 (av. 12:1) for the trimethylsilyl derivative.

Subsequent elution with C_6H_6–$CHCl_3$ (3:1, 7:1) afforded a mixture of pulchellins (I:II *ca.* 6:1, estimated by GLC and NMR analyses for the acetates), m.p. 158–68°, in a yield of 2·443 g (0·00009%), which has already been separated into pulchellin(I) and neopulchellin(II). Trituration of most of the fractions of the middle cut with EtOAc gave crude pulchellin (prisms, m.p. 152–62°), and an unidentified basic principle (pillars, m.p. 140–2°) which deposited from the mother liquor of the crystallization in a yield of 4·079 g (0·00015%) and 3·339 g (0·00012%), respectively. The final elution with $CHCl_3$–MeOH (99:1) afforded only the pulchellin mixture, m.p. 159–66° (I:II *ca.* 5:1, estimated as previously), 6·518 g (0·00024%). Total yield of pulchellin mixture and the basic substance ($C_{10}H_{19}O_{11}N_3$, m.p. 147–7·5°) were 11·95 g (0·00044%) and 4·43 g (0·00016%), respectively.

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