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NEW PSEUDOGUAIANOLIDES FROM *GAILLARDIA PULCHELLA**

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Abstract—In addition to pulchellin B and C previously isolated from a New Mexico race of *Gaillardia pulchella* Foug., the above-ground parts of an Arizona collection of this species furnished two new substances, pulchellin E and pulchellin F, whose structures have been established.

EXTRACTION of a collection of *Gaillardia pulchella* Foug. from Eastern New Mexico furnished[1] the pseudoguaianolides pulchellin B (Ib), pulchellin C (Ia) and pulchellin D (probably II) rather than pulchellin (III), the main sesquiterpene lactone of south-eastern races of *G. pulchella*.[2] The south-eastern races of this species are morphologically and cytologically identical with races found on the Gulf coast of Texas and Louisiana, but differ in these respects from races found farther west.[3] These differences appear to be reflected in the sesquiterpene lactone content.[4]

In an effort to secure more pulchellin B, C and D for chemical work, we extracted a large collection of *G. pulchella* from Arizona which, we had reason to believe, was closely allied to the earlier[1] material from New Mexico. This expectation was borne out by the results. Pulchellin C was the main sesquiterpene lactone constituent and was accompanied by pulchellin B. Pulchellin D could not be identified[5] among the constituents, but two new pseudoguaianolides of the pulchellin C family, pulchellin E and pulchellin F, were isolated and characterized as Ic and Id.

Pulchellin E, $C_{17}H_{22}O_5$, m.p. 181–183°, $[\alpha]_D^{28} + 43{\cdot}8°$, had spectral properties (see Experimental section) which indicated that it was 2-acetylpulchellin C (Ic). More specifically, a comparison of its NMR spectrum with that of pulchellin B (Ib) indicated that the somewhat broadened doublet of H-2 had shifted downfield from 4·0 to 5·08 and the H-3 multiplet had shifted upfield from 4·85 to 3·73 ppm, the remaining signals remaining essentially the same. The supposition was confirmed by acetylation of pulchellin E to diacetylpulchellin C (Ie) and by the conversion of tetrahydropulchellin E (Vb) to diacetyltetrahydropulchellin C (Va).

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*Part VII in the series "Constituents of *Gaillardia* Species." Previous paper, W. HERZ, P. S. SUBRAMANIAM and T. A. GEISSMAN, *J. Org. Chem.* **33**, 3743 (1968).

[1] W. HERZ and S. INAYAMA, *Tetrahedron* **20**, 341 (1964).

[2] W. HERZ, K. UEDA and S. INAYAMA, *Tetrahedron* **19**, 483 (1963).

[3] Private communication from Dr. W. P. STOUTAMIRE. That *G. pulchella* collections from the Texas Gulf coast are also chemically identical with the south-eastern races has been shown by Mr. P. W. Herz in our laboratory.

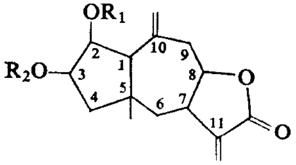
[4] S. M. KUPCHAN, J. M. CASSADY, J. E. KELSEY, H. K. SCHNOES, D. H. SMITH and A. L. BURLINGAME, *J. Am. Chem. Soc.* **88**, 5292 (1966). These authors described the isolation of a guaianolide gaillardin (IV) from a Live Oak County, Texas, collection. This is an area from which a cytologically distinct race of *G. pulchella* has been reported.[3]

[5] Only a very small amount of this substance has been isolated from the New Mexico collection.[1]

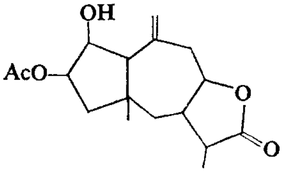
The empirical formula of pulchellin F, $C_{20}H_{32}O_5$, m.p. 144–146°, $[\alpha]_D^{28}+91{\cdot}7°$, and i.r. spectrum which contained an ester frequency at 1720 instead of the usual 1740 cm^{-1}, suggested the presence of a five-carbon unsaturated side-chain. The nature and point of attachment was indicated by the NMR spectrum which contained an additional vinyl proton multiplet at 6·08 and methyl signals at 1·90 and 1·88 ppm, all characteristic of an angeloyl group, as well as the broadened H-2 doublet at 4·06 and the H-3 multiplet at 4·9 ppm (cf. the NMR spectrum of pulchellin B[1]).

Hydrogenation of pulchellin F resulted in the saturation of three double bonds and the spectral changes expected on the basis of formula Id. The product, presumably Vc, had a secondary hydroxyl group because of a NMR signal (doublet of doublets) at 3·60 ppm which moved downfield to 4·83 ppm on acetylation and disappeared on oxidation with chromic oxide. In the NMR spectrum of the resulting cyclopentanone, the signal ascribed to H-3 had collapsed to a doublet of doublets, thus requiring a distribution of functional groups in the five-membered ring as in VI.

Final proof of structure Id for pulchellin F was provided by mild base-catalyzed hydrolysis of the substance to pulchellin C (Ic) and tiglic acid.



(Ia) $R_1, R_2 = H$
(Ib) $R_1 = H, R_2 = Ac$
(Ic) $R_1 = Ac, R_2 = H$
(Id) $R_1 = H, R_2 =$ angeloyl
(Ie) $R_1, R_2 = Ac$
(If) $R_1 = Ac, R_2 =$ angeloyl



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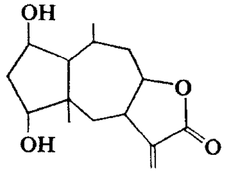

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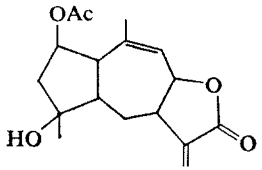
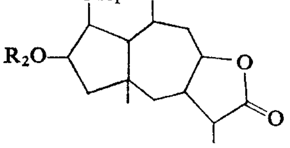
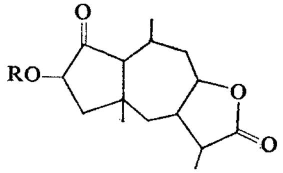


(IV)



(Va) $R_1, R_2 = Ac$
(Vb) $R_1 = H, R_2 = Ac$
(Vc) $R_1 = H, R_2 =$ α-methyl-isobutyryl
(Vd) $R_1 = Ac, R_2 =$ α-methyl-isobutyryl



(VI)

EXPERIMENTAL

M.ps were taken in a capillary melting point apparatus and are uncorrected. NMR spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as internal standard and are reported in ppm, multiplicities being indicated by the usual symbols (br slightly broadened singlet, d doublet, t triplet, m multiplet whose center is given). Line separations are in parentheses. I.r. spectra were run on a Perkin-Elmer infracord instrument.

Extraction of Gaillardia pulchella *Foug.*

Ground whole plant, collected by Mr. R. J. Barr on June 8, 9 and 15, 1963, along U.S. 80 in Cochise County, Arizona (Barr No. 62–362, voucher deposited in herbarium of Florida State University), wt. 20·8 kg, was extracted with $CHCl_3$ and worked up in the usual way yielding 835 g of crude gum. A 165-g portion was taken up in benzene–$CHCl_3$ (1:1) and chromatographed over 1·7 kg of alumina (Alcoa H-20) deposited with benzene–$CHCl_3$ (1:1). The chromatogram was successively eluted in 250-ml portions with 29 fractions of benzene–$CHCl_3$ (1:1), 14 fractions of benzene–$CHCl_3$ (2:1), 134 fractions of $CHCl_3$, 5 fractions of $CHCl_3$–methanol (100:1), 10 fractions of $CHCl_3$–methanol (50:1), 10 fractions of $CHCl_3$–methanol (100:3), 20 fractions of $CHCl_3$–methanol (20:1), 16 fractions of $CHCl_3$–methanol (10:1), 13 fractions of $CHCl_3$–methanol (5:1) and 8 fractions of $CHCl_3$–methanol (1:1), all fractions being monitored by TLC. Fraction 1–4 (1·51 g) could not be induced to solidify, fr. 5–8 gave 7·9 g of a mixture of pulchellin B and pulchellin F which was rechromatographed over 150 g of acid-washed alumina with 100-ml fractions of benzene–chloroform (1:1). Fractions 5–6 of this chromatogram gave 0·95 g of pulchellin F, fractions 7–11 yielded 1·3 g of pulchellin B.

Fractions 9–10 of the large-scale chromatogram gave 2·5 g of a mixture of pulchellin B, E and F. Rechromatography over 220 g of acid-washed alumina (100-ml fractions) gave in fractions 12–14 (benzene–$CHCl_3$ 2:1) 0·25 g of pulchellin F, in fractions 15–22 (benzene–$CHCl_3$ 1:1) 0·6 g of pulchellin B and in fractions 25–40 (benzene–$CHCl_3$ 1:2) 0·67 g of pulchellin B.

Fractions 11–19 of the large-scale chromatogram gave 5·807 g of a mixture of pulchellin B and E. Rechromatography over 250 g of acid-washed alumina (100-ml fractions) gave in fractions 6–13 (benzene–$CHCl_3$ 1:1) 1·1 g of pulchellin B and in fractions 17–22 (benzene–$CHCl_3$ 1:2) 1·3 g of pulchellin E.

Fractions 20–35 of the large-scale chromatogram could not be induced to solidify. Fractions 36–253 yielded only pulchellin C, mainly in the $CHCl_3$ eluate, total yield of unrecrystallized material 44·2 g. Fractions 254–261 and the polar gum obtained by washing the column with methanol, total wt. 5·8 g, contained a mixture of pulchellin C and two dimeric substances. Rechromatography of this gum over silicic acid with $CHCl_3$ and $CHCl_3$–methanol (50:1 and 20:1) gave in the $CHCl_3$ eluate small amounts of a dimeric substance *X*, m.p. 170–172°, λ_{max} 203 nm, i.r. bands (KBr) 350 (—OH), 1770, 1760 and 1660 cm^{-1}, and in the $CHCl_3$–methanol (20:1) small amounts of a dimeric substance *Y*, m.p. 116–118°, u.v. end absorption, i.r. bands ($CHCl_3$) 3600, 1775 and 1745 cm^{-1}. Elution with increasing proportions of methanol gave gums which could not be induced to crystallize.

The properties of pulchellin B and pulchellin C have been described previously. Pulchellin E was recrystallized from acetone–petroleum ether and had m.p. 181–183°, $[\alpha]_D^{28}+43{\cdot}80°$ (*c* 1·05, ethanol), λ_{max} 210 nm (ϵ 14,000), i.r. bands at 3620, 3510 (—OH), 1760 (γ-lactone), 1740 (acetate), 1660 and 1650 cm^{-1} (double bonds), NMR signals at 6·18d and 5·66d (1, exocyclic methylene conjugated with lactone), 5·08dbr (11, H-2), 4·98br and 4·70br ($=CH_2$), 4·56td (5, 2, H-8), 3·73m (H-3), 3·05m (H-7), 2·18 (acetate) and 0·89 ppm (C-5 methyl). (Found: C, 66·46; H, 7·42; O, 26·35. Calc. for $C_{17}H_{22}O_5$: C, 66·65; H, 7·24; O, 26·11.)

Acetylation of 0·2 g of pulchellin E with pyridine–acetic anhydride gave 0·135 g of crude solid. Recrystallization from acetone–petroleum ether gave material which had m.p. 188–191°, and was identical with diacetylpulchellin C in all respects (mixed m.p., TLC, i.r. and NMR spectrum).

Pulchellin F was recrystallized from acetone–petroleum ether and had m.p. 144–146°, $[\alpha]_D^{28}+91{\cdot}66$ (*c* 1·08, $CHCl_3$], λ_{max} 214 nm (ϵ 12,800), i.r. bands at 3560 (—OH), 1760 (γ-lactone), 1720 (ester) and 1650 cm^{-1} (double bond), NMR signals at 6·19d and 5·65d (1, conjugated exocyclic methylene), 6·08m (vinyl H of angelate side-chain), 5·43br and 4·80br (exocyclic methylene), the latter superimposed on 4·9m (H-3), 4·50td (6, 2, H-8), 4·06dbr (10, H-2), 3·0m (H-7), 1·90dq and 1·88 (vinyl methyls of side-chain) and 0·95 ppm (C-5 methyl). (Found: C, 69·01; H, 8·07; O, 22·91. Calc. for $C_{20}H_{26}O$: C, 69·34; H, 7·57; O, 23·09.)

Tetrahydropulchellin E

A solution of 0·3 g of pulchellin E in 50 ml of methanol was hydrogenated with 0·06 g of PtO_2 at 32 lb/in^2 for 18 hr. The solvent was evaporated at reduced pressure. The residue was recrystallized from acetone–hexane and had m.p. 169–171°, i.r. bands at 1770 (γ-lactone) and 1740 cm^{-1} (acetate), NMR signals at 4·53dd (11, 6, H-2), 4·24m (H-8), 3·86td (11, 4·5, H-3), 2·05 (acetate), 1·12d (7, C-10 methyl), 0·99 (C-5 methyl) and 0·83d ppm (7, C-10 methyl). (Found C, 65·56; H, 8·72; O, 25·61. Calc. for $C_{17}H_{26}O_5$; C, 65·78; H, 8·44; O, 25·78.)

Acetylation of 0·2 g of tetrahydropulchellin E furnished 0·12 g of a monoacetyl derivative, m.p. 226–227°, identical with diacetylpulchellin C (mixed m.p., TLC, i.r. and NMR spectrum).

Acetylpulchellin F

Acetylation of 0·2 g of pulchellin F with acetic anhydride and pyridine yielded 0·1 g of solid which was recrystallized from acetone–hexane and had m.p. 130–132°, i.r. bands at 1765 (double intensity, lactone and ester), 1725 (acetate) and 1655 cm^{-1} (double bond), NMR signals at 6·11d and 5·60d (1, conjugated exocyclic methylene), 5·95m (vinyl proton of side chain), 5·43dbr (10, H-2), 5·00br and 4·70br (unconjugated exocyclic methylene), 4·95m (H-3), 4·5td (5, 2, H-8), 3·0m (H-7), 2·08 (acetate), 1·98dq and 1·85 (vinyl methyls of side chain) and 0·95 ppm (C-5 methyl). (Found: C, 68·23; H, 7·10, O, 24·88. Calc. for $C_{22}H_{28}O_6$: C, 68·02; H, 7·27; O, 24·71.)

Hexahydropulchellin F

A solution of 0·2 g of pulchellin F in 30 ml of methanol was shaken with 40 mg of PtO_2 in H_2 (32 lb/in^2) for 12 hr, filtered and evaporated *in vacuo*. The residual solid, wt. 0·185 g, was recrystallized from acetone–hexane and had m.p. 153–154°, i.r. bands at 3600 (—OH), 1770 (γ-lactone) and 1740 cm^{-1} (ester), NMR signals at 4·88td (10, 4, H-3), 4·33m (H-8), 3·60dd (10, 5, H-2), 1·26–0·85 ppm (five superimposed methyls). (Found: C, 68·06; H, 9·15; O, 22·90. Calc. for $C_{20}H_{32}O_5$: C, 68·15; H, 9·15; O, 22·70.)

Acetylation of 0·3 g of this compound gave 0·25 g of acetylhexahydropulchellin F which was recrystallized from acetone–hexane and had m.p. 180–182°, i.r. bands at 1775 (γ-lactone) and 1740 cm^{-1} (double intensity, acetate and ester), NMR signals at 5·16td (11, 5, H-3), 4·83dd (11, 5), 4·36m (H-8), 1·95 (acetate and 1·19–0·83 (five superimposed methyls). (Found: C, 67·08; H, 8·42; O, 24·72. Calc. for $C_{22}H_{34}O_6$: C, 66·98; H, 8·69; 0, 24·34.)

Dehydrohexahydropulchellin F

A solution of 0·2 g of hexahydropulchellin F in 2·5 ml of acetic acid was mixed with 0·2 g Cr_2O_3 in 2·5 ml of acetic acid and a few drops of water and allowed to stand overnight with stirring. Excess oxidizing agent was destroyed with methanol and the solvent removed at reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried and evaporated. The residue, wt. 0·15 g, could not be induced to crystallize but TLC indicated that only one compound was present. Chromatography over silicic acid and elution with benzene yielded sticky semisolid material homogeneous by TLC and NMR criteria, NMR signal at 5·47dd (14, 6, H-3), 4·42m (H-8), and 1·3–1·1 ppm (five methyls).

Hydrolysis of Pulchellin F

A mixture of 0·26 g of pulchellin F and 35 ml of 5 N alcoholic KOH was left overnight and then concentrated *in vacuo*. The residue was mixed with 1 N H_2SO_4 and steam distilled. The steam distillate was extracted with $CHCl_3$, but no residue was obtained on evaporation of this extract. The residue of the steam distillation was basified and extracted with $CHCl_3$. The extract was washed, dried and evaporated; the residue, m.p. 189–194°, on recrystallization from acetone–hexane, afforded material of m.p. 195–198° which was identical with pulchellin C (TLC, m.p., mixed m.p., i.r. spectrum). The basic water layer from the $CHCl_3$ extraction was evaporated *in vacuo*, the residue acidified with 1 N H_2SO_4 and thoroughly extracted with ether. The combined ether extracts were washed, dried and evaporated. The residue, wt. 25 mg, on recrystallization furnished tiglic acid which was identified by direct comparison with an authentic sample and through the cyclohexylamine salt.

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