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PHACIDIN, A NOVEL γ-PYRONE FUNGAL GROWTH INHIBITOR FROM POTEBNIAMYCES BALSAMICOLA VAR BOYCEI

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Phacidin has been isolated from liquid culture of the canker fungus Potebniamyces balsamicola Smerlis var. boycei Funk, and has been shown to have strong inhibitory effects on the growth of a wide variety of fungi[1]. Phacidin is obtained as yellow crystals, mp 112-113°, affords a phenylhydrazone (mp 178°) on treatment with phenylhydrazine hydrochloride, and exhibits a positive Tollens' Test. High resolution mass spectrometry confirms the molecular formula $C_{16}H_{22}O_5$ (found: 294.151; calculated for $^{12}C_{16}{}^{1}H_{22}{}^{16}O_5$; 294.147); elemental analysis C: 65.10, H: 7.62% (calculated C: 65.29, H: 7.53%). Phacidin is optically inactive.

The presence of a γ-pyrone nucleus may be inferred from the infra-red absorption at 1690 (C=O), 1620, 1530, 1520 (C=C) and 1235 cm^{-1} (C-O-C), and from the ultra-violet maxima[2] at 225 (log ε = 4.34), 279 (3.99) and 320 nm (4.05). The trisubstituted nature of this ring is evident from the spectra: ν_{max}^{KBr} 846 cm^{-1}, δ^{CDCl_3} 7.11 (1H,s); the chemical shift of this proton is assignable to a proton at H_3 or H_5 of the γ-pyrone nucleus (*vide infra*).

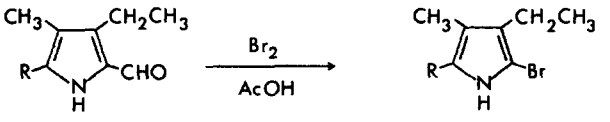
The IR, NMR, and mass spectra reveal that phacidin contains a methoxyl group [1478, 1235, 1041 cm^{-1}; δ4.11 (3H,s); m/e 121, 93 ($[153-32]^+$ and $[121-32]^+$, respectively)], a formyl group [2870, 1730 cm^{-1}; δ10.17 (1H,s); m/e 238, 237, 125 ($[266-28]^+$, $[266-29]^+$, and $[153-28]^+$, respectively)], and a third carbonyl group (ν_{max} 1700 cm^{-1}). The nature of this latter substituent was determined by oxidation of phacidin by hydrogen peroxide, neutral $KMnO_4$, or ruthenium tetroxide to yield n-nonanoic acid, identical in all respects with an authentic sample. The third substituent is thus an n-nonanoyl group: δ0.88 (3H,t), 1.1-2.0 (12H,m), and 2.96 (2H,t); m/e 141.128 ($[C_8H_{17}CO]^+$, calculated for $^{12}C_9{}^{1}H_{17}{}^{16}O_1$: 141.139) and 153.020 ($[M-141]^+$, calculated for $^{12}C_7{}^{1}H_5{}^{16}O_4$: 153.019).

The structure XXVI is assigned to phacidin on the basis of the following evidence:

i) The methoxyl group can be placed at C_2 on the basis of its lability towards acid[3], its characteristic δ value, and its mass spectral behavior; model γ-pyrones derived from maltol and kojic acid, having a C_3 methoxyl substituent, are relatively stable towards acid[4] and exhibit the OMe resonance in the NMR between δ 3.70 and 3.82. All model compounds bearing a C_3-OMe have been found [5] to exhibit $[M-18]^+$ peaks in the mass spectrum; phacidin does not.

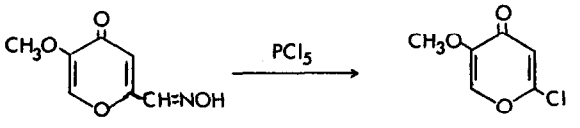
ii) A carbonyl substituent (CHO or COC_8H_{17}) must be placed at C_6, ortho to the C_5 hydrogen to account for the observed deshielding from the normal resonance position. As can be seen from the accompanying table, protons in the γ-pyrone nucleus are generally observed in the range δ 7.5 - 7.9 when located at positions 2 or 6, while those at positions 3 or 5 are found in the range δ 6.0 - 6.6. Adjacent carbonyl substitution would be expected to deshield such a proton: that this is so is evident from the chemical shift of H_3 in 5-methoxy-4-oxo-4H-pyran-2-carboxaldehyde (XXI). The observed deshielding (0.62 ppm) is comparable to that reported[13] for substituted furans (0.6 - 0.8 ppm). This magnitude of deshielding is not produced by an adjacent alkoxyl group (see compounds XIV, XV), nor is it evident when the carbonyl substituent is not present at an adjacent position (see compound XVI).

iii) We have assigned the formyl group to this position (C_2) on the basis of the following evidence: Bromination of phacidin leads to the formation of a bromo-deformyl derivative, as indicated by the loss of the aldehydic proton in the nmr spectrum, and the molecular weight of 345 as indicated by mass spectrometry (molecular ion doublet at 344/346, 8.5% of the base peaks 203/205). This is analogous to the reported[14] deformylation of the pyrrole derivative XXII to yield the 2-bromo-pyrrole XXIII



XXII XXIII

and is supported by our related replacement of a derivatized C_2-formyl substituent by halogen under mild conditions[15] (cf XXIV ⟶ XXV).



XXIV XXV

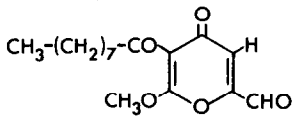
TABLE

CHEMICAL SHIFTS* OF A SERIES OF SUBSTITUTED γ-PYRONES

Compound No.	R_2	R_3	R_5	R_6	$H_{2,6}$	$H_{3,5}$	Reference
I	H	H	H	H	7.71	6.35	6
II	CH_3	H	H	Ph		6.19(3),6.69(5)	6
III	CH_3	H	H	CH_3		6.04	6
IV	CH_3	OH	H	H	7.73	6.43	6
V	CH_3	OCH_3	H	H	7.89	6.23	7
VI	H	CH_3	H	H	7.52	6.15	8
VII	CH_3	OH	H	CH_3		6.25	9
VIII	OCH_2CH_3	H	H	CH_3		5.95(5)	10
IX	OCH_2CH_3	CH_3	H	CH_3		5.96	10
X	OCH_2CH_3	Ph	H	CH_3		6.10	10
XI	OCH_2CH_3	Cl	H	CH_3		6.10	10
XII	OCH_2CH_3	Br	H	CH_3		6.10	10
XIII	OCH_2CH_3	CN	H	CH_3		6.10	10
XIV	OCH_3	H	H	$CH=C(OCH_3)Ph$		5.5(3),6.8(5)	11
XV	OCH_3	H	H	CH_3		5.49(3),6.01(5)	12
XVI	CH_3	COOH	H	CH_3		6.39	This work
XVII	CH_2OCH_3	H	OCH_3	H	7.59	6.45	This work
XVIII	CH_2OTHP	H	OCH_3	H	7.59	6.52	This work
XIX	CH_2Cl	H	OH	H	7.86	6.56	This work
XX	CH_2OCH_3	H	OH	H	7.85	6.51	This work
XXI	CHO	H	OCH_3	H	7.69	6.97	This work

* all chemical shifts measured in $CDCl_3$ or CCl_4, with TMS as internal standard.

The nonanoyl group must then occupy the C_3 position, and phacidin is thus 6-methoxy-5-nonanoyl-4-oxo-4H-pyran-2-carboxaldehyde (XXVI).



XXVI

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Footnotes & References:

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