Pergamon 0031–9422(94)00699–7

Phytochemistry, Vol. 38, No. 2, pp. 491–493, 1995
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0031–9422/95 $9.50 + 0.00

SYNTHESES OF 2,4,6-TRIHYDROXY-, 2,4,6-TRIHYDROXY-5-METHYL- AND 2,4,5,6-TETRAHYDROXY-SUBSTITUTED 3-(3-PHENYLPROPIONYL)BENZALDEHYDES AND THEIR BACTERICIDAL ACTIVITY

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(*Received* 17 *June* 1994)

Key Word Index—Antifungal activity; antifeedant activity: bactericidal activity; 2,4,6-trihydroxy- and 2,4,6-trihydroxy-5-methyl-substituted 3-(3-phenylpropionyl)benzaldehydes.

Abstract—2,4,6-Trihydroxy-, 2,4,6-trihydroxy-5-methyl-, and 2,4,5,6-tetrahydroxy-substituted 3-(3-phenylpropionyl)benzaldehydes were efficiently synthesized. The first two compounds showed bactericidal activity for *Pseudoperonospora cubersis.*

INTRODUCTION

In 1990, 2,4,5-trihydroxy- and 2,4,6-trihydroxy-5-methyl-substituted 3-(3-phenylpropionyl) benzaldehydes (**1**, **2**), which showed potent antifungal activity, were isolated from the leaves of *Psidium actangulum* by Miles *et al.* [1, 2]. Compound **2** was shown to have antifeedant activity against tobacco budworm (*Heliothis virescens*) [1]. Both compounds are the first natural 2,4,6-trihydroxy-3-(3-phenylpropionyl)benzaldehydes [2]. In this paper, we describe an efficient first synthesis of these naturally occurring 3-(3-phenylpropionyl)benzaldehydes and an analogous compound **3** by using Hoesch and Gattermann reactions, and we report on their bactericidal activity.

RESULTS

As shown in Scheme 1, **1** was synthesized by Hoesch reaction of 1,3,5-benzenetriol with 3-phenylpropionitrile, followed by Gatterman reaction with zinc cyanide. Compound **3**, which has one more hydroxyl group, was also synthesized by the same method from 1,2,3,5-benzenetetrol [3]. Next, **2** was synthesized by regioselective Clemmensen reduction of **1** [4] followed by Gatterman reaction with zinc cyanide. The yeild of each reaction was satisfactory. The bactericidal activity of these compounds is shown in Table 1. Compounds **1** and **2** were active against *Pseudoperonospora cubensis*, while **3** showed only weak bactericidal activity.

EXPERIMENTAL

Biological assay. To each young plant having a few leaves e.g. cucumber, wheat, tomato, and kidney bean, an aq. soln or suspension of compounds (**1**–**6**) was spread and air-dried. Subsequently, the resulting plants were innoculated by each bacteria as described in Table 1 respectively. After standing for 3–14 days, each plant was observed and assessed, as shown.

All mps: uncorr.

3-*Phenyl*-1-(2,4,6-*trihydroxyphenyl*)-1-*propanone* (**4**). Into a mixt. of 1,3,5-benzenetriol (5 g, 39.7 mmol), 3-phenylpropionitrile (8.45 g, 64.5 mmol), and zinc chloride (1.97 g, 14.5 mmol) in dry ether (100 ml) was passed dry HCl gas under vigorous stirring by a mechanical stirrer and under cooling with an ice-salt bath (− 10 to − 15 °C) for 3 hr. The reaction mixt. was allowed to stand overnight in a freezer, and again dry HCl gas passed through it. After further standing in a freezer, the reaction mixt. was decanted and the residual brown viscous syrup was hydrolysed by refluxing in H_2O (150 ml) for 2 hr. After filtration, the yellow residue was recrystallized from $CHCl_3$ twice to give 9.0 g (88%) of **4** as needles. Mp 142–143°. MS (25 eV) *m/z* 258 $[M]^+$. IR (KBr) 3400 (OH), 1600 (C = O) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ3.01 (2H, *m*, β-CH_2), 3.33 (2H, *m*, α-CH_2), 5.87 (2H, *s*, 5′-ArH), 7.24 (5H, *s*, ArH), 9.88 (1H, *s*, 4′-OH), 11.98 (2H, *s*, 2′- and 6′-OH). Found: C, 69.60; H, 5.54%; Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46%.

3-*Phenyl*-1-(2,3,4,6-*tetrahydroxyphenyl*)-1-*propanone* (**5**). This compound was synthesized in a similar manner as described above. Yield 94%. Pale-yellow needles. Mp 141–142°. MS (25 eV) *m/z* 274 $[M]^+$. IR (KBr) 3400 (OH), 1640 (C = O), and 1440 cm^{-1}. ^{1}H NMR (DMSO-d_6: δ2.92 (2H, *m*, β-CH_2), 3.31 (2H, *m*, β-CH_2), 5.93 (1H, *s*,

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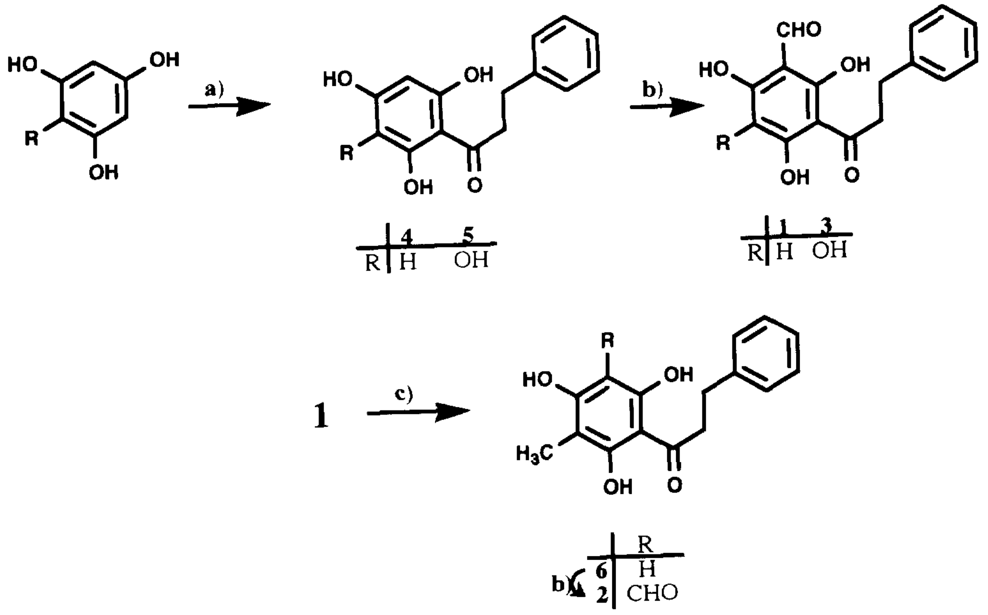

Scheme 1. (a) (i) $PhCH_2CH_2CN$, $ZnCl_2$, in ether, HCl (gas), (ii) H_2O, reflux. (b) (i) $Zn(CN)_2$, $AlCl_3$, in ether, HCl (gas), (ii) H_2O, reflux. (c) Zn(Hg), HCl, MeOH, 50°, 15 min.

Table 1. Bactericidal activity test

Compounds	P. c	E. g	P. i	B. c	P. r
	Disease (0: normal, 5; completely damaged)				
1	0.7	3	3.8	4.1	2
2	0.8	4	4.2	5	3
3	2.7	5	5	5	5
4	4	5	5	3.8	4
6	3.2	5	5	5	5
Control	5	5	5	5	5

Concentration of these compounds was 500 ppm.
P. c: *Pseudoperonospora cubensis.*
E. g: *Erisiphe graminis.*
P. i: *Phytophthora infestans.*
B. c: *Botrytis cinerea.*
P. r: *Puccinia recondita.*

5'-H), 7.24 (5H, *s*, ArH), 10.09 (1H, *s*, OH), 11.30 and 12.14 (each 1H, *s*, OH). Found: C, 65.55; H, 5.04%; Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14%.

2,4,6-*Trihydroxy*-3-(3-*phenylpropionyl*)*benzaldehyde* (**1**). Into a vigorously stirred soln of **4** (5 g, 19.4 mmol), zinc cyanide (4.45 g, 38.7 mmol) and aluminium chloride (95.2 g, 38.7 mmol) in dry ether (100 ml) was passed dry HCl gas under cooling with an ice-salt bath (−10 to −15°) for 3 hr. The reaction mixt. was allowed to stand overnight in a freezer. This operation was repeated once more. After decantation, the residual brown viscous syrup was refluxed in H_2O (100 ml) for 1 hr. After filtration, the yellow residue was dissolved in EtOAc. The EtOAc soln was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and then concd to give reddish brown syrup, which was recrystallized from EtOAc (×3) to give 2.47 g (45%) of **1** as prisms. Mp 157–158° (lit. [1] 152–153°). MS (25 eV) *m/z* 286 $[M]^+$. IR (KBr) 3450 and 3100 (OH), 1630 and 1605 (C = O), and 1440 cm^{-1}. UV (MeOH) 325 (ε 5400), 269 (32 600) nm. ^1H NMR ($CDCl_3$): δ3.06 (2H, *m*, β-CH_2), 3.43 (2H, *m*, α-CH_2), 5.83 (1H, *s*, 5'-H), 7.26 (5H, *s*, ArH), 10.10 (1H, *s*, CHO), 14.42 and 14.84 (each 1H, *s*, OH). Found: C, 67.29; H, 4.97%; Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93%.

2,4,5,6-*Tetrahydroxy*-3-(3-*phenylpropionyl*)*benzaldehyde* (**3**). This compound was synthesized in a similar manner as described above. Needles. Yield; 72%. Mp 174–175°. MS (25 eV) *m/z* 302 $[M]^+$. IR (KBr) 3450 (OH), 1640, 1620 (C = O) and 1450 cm^{-1}. UV (MeOH) 275 (ε 36 300), 360 (7500) nm. ^1H NMR (DMSO-d_6): δ2.94 (2H, *m*, β-CH_2), 3.34 (2H, *m*, α-CH_2), 7.27 (5H, *s*, ArH), 10.05 (1H, *s*, CHO), 12.44 and 14.32 (each 1H, *s*, OH). Found: C, 63.70; H, 4.55%; Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67%.

1-(2,4,6-*Trihydroxy*-3-*methyl*)*phenyl*-3-*phenyl*-1-*propanone* (**6**). A soln of **1** (1.15 g, 4.02 mmol) in MeOH (40 ml), zinc amalgum (110 g), conc HCl (20 ml) and H_2O (5 ml) was heated at 50° for 15 min. After decantation for removing zinc amalgum, 50 ml of H_2O was added to the supernatant soln. The mixt. was extracted with EtOAc twice. The combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and concd under red. pres. The residual pale-yellow crude crystals were recrystallized from $CHCl_3$ to give 0.80 g (73%) of **6** as pale-yellow needles. Mp 178–179°. MS (25 eV) *m/z* 300 $[M]^+$. IR (KBr) 3400 (OH), 2930, 1610 (C = O), 1450, 1380 and 1180 cm^{-1}. ^1H NMR ($CDCl_3$): δ2.04 (3H, *s*, Me), 3.05 (2H, *m*, β-CH_2), 3.42 (2H, *m*, α-CH_2), 7.27 (5H, *s*, ArH), 10.15 (1H, *s*, CHO), 14.37 and 15.25 (each 1H, *s*, OH). Found: C, 67.90; H, 5.39%, Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%.

2,4,6-Trihydroxy-3-methyl-5-(3-phenylpropionyl)benzaldehyde (**2**). This compound was synthesized in a similar manner as that of **1**. Yield 54%. Needles. Mp 157–158° (lit. [1] 157–158°). MS (25 eV) *m/z* 300 $[M]^+$. IR (KBr) 3400 (OH), 2930, 1620 (C = O) cm^{-1}. UV (MeOH) 272 (ε 34400) and 337 (4600) nm. ^1H NMR ($CDCl_3$): ε2.04 (3H, *s*, Me), 3.05 (2H, *m*, β-CH_2), 3.42 (2H, *m*, α-CH_2), 7.27 (5H, *s*, ArH), 10.15 (1H, *s*, CHO), 14.37 and 15.25 (each 1H, *s*, OH). Found: C, 67.90; H, 5.39%; Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%.

Acknowledgements—The authors are grateful to Prof. D. Howard Miles of University of Central Florida, for the comparison of our synthetic samples with the natural specimens. We also would like to thank Mr Kazuaki Sato for the elemental analysis.

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