Synthesis of Quinolactacide via an Acyl Migration Reaction and Dehydrogenation with Manganese Dioxide, and Its Insecticidal Activities

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Quinolactacide isolated from Penicillium citrinum F1539 was synthesized and evaluated for its insecticidal activities. The key steps of the total synthesis were an acyl migration reaction of the enol ester intermediate and dehydrogenation of tetrahydroquinolactacide with manganese dioxide. The synthesized quinolactacide showed 100% and 42% mortality against the green peach aphid (Myzus persicae) and diamondback moth (Plutella xylostella) at 500 ppm, respectively.

Key words: quinolactacide; insecticidal activity; acyl migration reaction; dehydrogenation

In our previous study,1) we have reported the isolation of a new insecticidal quinolone, quinolactacide (1), from Penicillium citrinum Thom F 1539 and determined its chemical structure (Fig. 1). Quinolactacide (1) showed 88% mortality against the green peach aphid (Myzus persicae) at 250 ppm. However, we could not conduct further biological tests due to the limited amount of the isolated compound. We therefore started a synthetic study on quinolactacide (1) to obtain a sufficient amount of the compound.

Quinolactacide (1) is structurally related to quinolactacins (2–6) isolated from Penicillium sp., which are known to show some biological activities.2–5) The synthesis of racemic quinolactacin B and enantioselective syntheses of quinolactacins A and B have also been reported,6,7) but there was no description on their insecticidal activity in the reports.

We report here the first total synthesis of quinolactacide (1) and its insecticidal activities.

The synthetic route used for quinolactacide (1) is shown in Scheme 1. Proline ethyl ester 8 was prepared by esterification of L-proline (7) in ethanol with thionyl chloride. The amino group of 8 was acetylated with acetyl chloride and pyridine in tetrahydrofuran (THF) to give 9. The cyclopenta-1,3-dione ring was successfully constructed by Dieckmann-type cyclization to give 10 in a 59% yield.8) Esterification of 1,3-dione 10 with triethylamine (TEA) and 2-nitrobenzoyl chloride afforded enol ester 11.9) Acyl migration of 11 catalyzed with acetone cyanohydrin proceeded quantitatively to give trione 12.9) Hydrogenation of the nitro group of trione 12 resulted in spontaneous cyclization to give tetrahydroquinolactacide 13 in a 52% yield. Compound 13 showed poor solubility in almost all organic solvents, including dimethyl sulfoxide (DMSO), so 13 was suspended in a mixture of chloroform and N,N-dimethylformamide (DMF) and dehydrogenated with manganese dioxide (MnO2) to give quinolactacide (1) in a 21% yield.10) Starting compound 13 was not found in the reaction mixture. In an attempt to improve the yield of the dehydrogenation reaction, the reaction was conducted...

Fig. 1. Structures of Quinolactacide (1) and Related Compounds, Quinolactacins (2–6).
with MnO₂ in a mixture of chloroform and methanol, because of the good solubility of compound 13 in the mixed solvent, and also carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the same mixed solvent, but both reactions did not proceed well. Although the yield of the dehydrogenation reaction was not improved, sufficient quinolactacide (1) was obtained for further biological tests. The physico-chemical properties of synthetic 1 were identical with those of the natural compound.

The insecticidal and the miticidal activities of quinolactacide (1) against five different insects and one mite were evaluated at 500 ppm. The insects used for the tests were the green peach aphid (1), diamondback moth (Plutella xylostella), common cutworm (Spodoptera litura), silverleaf whitefly (Frankliniella occidentalis), and two-spotted spider mite (Tetranychus urticae). Synthetic quinolactacide (1) showed 100% and 42% mortality against the green peach aphid and diamondback moth, respectively, but did not show any activity against the others.

Our future study will be focused on the structure-activity relationships between quinolactacide (1) and its related compounds, and their insecticidal activity.

**Experimental**

**General.** The following instruments were used in the experiments: a Bruker DPX 300 FT NMR (300 MHz) spectrometer for the 1H-, 13C-NMR, and DEPT spectra, a Jeol The MStation JMS-700 mass spectrometer for the mass spectra, a Shimadzu FTIR-8100A IR spectrometer for the IR spectra, a Shimadzu UV-160 UV–VIS recording spectrophotometer for the UV spectra, and Büchi B-545 melting point apparatus for measuring the melting point (mp). The NMR spectra were measured by using CDCl₃ containing 0.03% tetramethylsilane (TMS) or DMSO-d₆ as a solvent. Kanto Chemical 60N silica gel (spherical, neutral, 100–200μm) was used for column chromatography. The optical purity of intermediates 8–13 was not measured. The insecticidal test against the green peach aphid was conducted in the same manner as that described in our previous report, and against the silverleaf whitefly was conducted in almost the same manner as that against the aphid. In the test, first instar larvae of the silverleaf whitefly were treated with formulated quinolactacide (1), and the mortality was assessed after 6d. The insecticidal test against the common cutworm was conducted in almost the same manner as that against the diamondback moth, second instar larvae of the common cutworm being used for the test. The insecticidal test against the western flower thrips was conducted in almost the same manner as that against the two-spotted spider mite, fifteen first instar larvae of the western flower thrips being used for the test.

**Ethyl pyrrolidine-2-carboxylate (8).** To a solution of 7 (10.0 g, 87.0 mmol) in dry ethanol (200 ml) was added dropwise thionyl chloride (20.7 g, 174 mmol) at 60 °C. The mixture was refluxed for 4 h and then stirred for 12 h at 20 °C. The reaction mixture was concentrated under reduced pressure, neutralized with 4 mol NaOH (22 ml) at 0 °C and then successively extracted with ethyl acetate (EtOAc) and chloroform. Each organic layer was washed with brine and dried over anhydrous MgSO₄. The combined organic layers were concentrated to afford 8 (12.5 g, quant.) as a pale yellow oil. The crude product thus obtained was used for the next step without further purification. ¹H-NMR (CDCl₃, TMS) δ: 1.28 (3H, t, J = 7.1 Hz), 1.70–1.90 (3H, m), 2.05–2.15 (1H, m), 2.90 (1H, dt, J = 10.3, 6.5 Hz), 3.08 (1H, dt, J = 10.3, 6.5 Hz), 3.74 (1H, dd, J = 8.5, 5.5 Hz), 4.18 (2H, q, J = 7.1 Hz); NH was not detected.

**Ethyl 1-acetylpyrrolidine-2-carboxylate (9).** To a mixture of compound 8 (8.00 g, 55.9 mmol) and pyridine (5.30 g, 67.1 mmol) in THF (150 ml) was added dropwise acetyl chloride (5.27 g, 67.1 mmol) dissolved in THF (10 ml) at 0 °C. The mixture was stirred for 1 h at 0 °C and then for 2 h at 20 °C. The reaction mixture was poured into 1 mol HCl (20 ml) at 0 °C and extracted with EtOAc. The EtOAc extract was successively washed with sat. NaHCO₃ and brine, dried over anhydrous...
MgSO₄, and concentrated to afford 9 (9.32 g, 90%) as a pale yellow oil. The crude product was used for the next step without further purification. IR (film) νmax cm⁻¹: 1740 (s), 1650 (s), 1420 (s), 1375 (m), 1360 (m), 1280 (m), 1240 (m), 1190 (s), 1090 (m), 1030 (m), 1000 (w), 920 (w), 620 (w), 540 (w). ¹H-NMR (CDCl₃, TMS) δ: 1.23–1.31 (3H, m), 1.85–2.40 (4H, m), 3.45–3.55 (1H, m), 3.61–3.75 (1H, m), 4.10–4.24 (2H, m), 3.38 (0.3H, dd, J = 8.5, 3.5 Hz), 4.47 (0.7H, dd, J = 8.5, 3.5 Hz).

HR-EIMS m/z (M⁺): calcd. for C₉H₁₂O₅N, 185.1052; found, 185.1054.

1-Azabicyclo[3.3.0]octane-2,4-dione (10). To a suspension of potassium tert-butoxide (1.36 g, 12.2 mmol) in a mixture of THF (10 ml) and dry toluene (10 ml) was added dropwise compound 9 (1.50 g, 8.11 mmol) dissolved in THF (10 ml) at 80 °C. The mixture was refluxed for 12 h. After cooling, the reaction mixture was successively extracted with water and 1 N NaOH. The combined water layers were acidified with 4 N HCl to pH 3 and successively extracted with EtOAc and chloroform. The organic layer was washed with brine and dried over anhydrous MgSO₄. The combined organic layers were concentrated to afford 10 (670 mg, 59%) as a brown oil. The crude product was used for the next step without further purification. IR (film) νmax cm⁻¹: 3430 (br. m), 2700 (br. m), 2600 (br. m), 1770 (s), 1690 (br. s), 1610 (br. s), 1420 (br. s), 1375 (br. s), 1320 (br. s), 1260 (m), 1230 (br. m), 1075 (w), 820 (w), 630 (w), 590 (w), 560 (w). ¹H-NMR (CDCl₃, TMS) δ: 1.65–1.75 (1H, m), 1.97–2.22 (3H, m), 3.02 (1H, dd, J = 21.4, 1.2 Hz), 3.15–3.25 (1H, m), 3.37 (1H, d, J = 21.4 Hz), 3.95 (1H, dt, J = 11.8, 7.5 Hz), 4.20 (1H, pseudo t, J = 8.5, 7.9 Hz). HR-EIMS m/z (M⁺): calcd. for C₁₄H₁₄O₅N, 240.0899; found, 240.0897.

1,2,3,11b-Tetrahydroquinolactacide (11). A solution of 10 (300 mg, 1.04 mmol) in methanol (15 ml) was vigorously stirred over Pd/C 10% (20 mg) under hydrogen at atmospheric pressure for 3 d at 20 °C. The reaction mixture was filtered and successively washed with methanol and chloroform. The combined filtrates were concentrated under reduced pressure. The crude solid thus obtained was washed with a mixture of methanol and EtOAc and dried in vacuo to give 11 (4.96 g, 80%) as a pale brown solid, mp 393–398 °C (dec.). IR (KBr) νmax cm⁻¹: 3700–2400 (br. w), 1690 (s), 1630 (s), 1620 (s), 1590 (s), 1540 (s), 1470 (s), 1420 (w), 1370 (m), 1340 (w), 1300 (m), 1280 (w), 1220 (m), 1170 (w), 1140 (w), 1090 (w), 1030 (w), 980 (w), 960 (w), 880 (w), 870 (w), 800 (w), 780 (m), 770 (m), 750 (m), 730 (m), 680 (m), 660 (m), 530 (m). ¹H-NMR (DMSO-d₆) δ: 1.38–1.56 (1H, m), 2.05–2.33 (3H, m), 3.05–3.18 (1H, m), 3.44 (1H, dt, J = 10.9, 8.2 Hz), 4.67 (1H, dd, J = 9.5, 6.5 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.56 (1H, d, J = 8.0 Hz), 7.71 (1H, dt, J = 8.0, 1.3 Hz), 8.15 (1H, d, J = 8.0 Hz), 12.72 (1H, br. s). HR-EIMS m/z (M⁺): calcd. for C₁₄H₁₂O₄N₂, 288.0746; found, 288.0736.
MnO₂, and then the mixture was refluxed for 12 h more. The reaction mixture was cooled to room temperature and chromatographed in a silica gel column by eluting with chloroform–methanol (30:1→15:1). The fraction containing quinolactacide (I) was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water to remove residual DMF, dried over anhydrous MgSO₄, and concentrated to give I as a yellow solid. Quinolactacide (I) was further washed with water to remove residual DMF, and dried in vacuo to give pure I (4.1 mg, 21%) as a yellow powder. To measure mp of I, the pure compound was prepared as a yellow powder by recrystallizing from a mixture of chloroform and methanol, mp (chloroform–methanol) 372–373 °C (dec.). IR (KBr) νmax cm⁻¹: 3440 (br. w, NH), 1740 (s, N–C=O), 1645 (s, C=O), 1620 (m), 1580 (s), 1540 (m), 1525 (m), 1475 (m), 1395 (w), 1220 (w), 1050 (w), 770 (m). UV (s), 1540 (m), 1525 (m), 1475 (m), 1395 (w), 1220 (w), 1050 (w), 770 (m). UV λmax (CHCl₃:CH₂OH = 1:1, 26 °C) nm (ε): 242.4 (12100), 288.1 (33900). ¹H-NMR (DMSO-d₆) δ: 6.37 (1H, t, J = 3.1 Hz), 6.72 (1H, d, J = 3.1 Hz), 7.38–7.45 (2H, m), 7.57 (1H, d, J = 8.2 Hz), 7.71 (1H, pseudo t, J = 8.2, 6.9 Hz), 8.12 (1H, d, J = 7.4 Hz), 13.25 (1H, br. s). EIMS m/z: 236 (M⁺), 208, 179, 168 (M⁺–C₆O₂). HR-EIMS m/z (M⁺): calcd. for C₁₄H₁₀O₂N₂, 236.0586; found, 236.0611.

Insecticidal test against the diamondback moth (Plutella xylostella). An insecticidal formulation (500 ppm) was prepared by adding an aqueous solution (100 ppm) of Sorpol 355 (Toho Chemical Industry, Tokyo, Japan) to a methanol solution containing a 1.25% DMSO solution of quinolactacide (I), and 4.0 ml of the formulation was sprayed over two excised leaf squares (5 x 5 cm) from a cabbage plant at the 6-leaf stage. After air-drying, fifteen third instar larvae of the diamondback moth were settled on the leaves, and the stage. After 4 d, an insecticidal formulation (500 ppm) was prepared by adding an aqueous solution (100 ppm) of Sorpol 355 (Toho Chemical Industry, Tokyo, Japan) to a methanol solution containing a 1.25% DMSO solution of quinolactacide (I), and 4.0 ml of the formulation was sprayed over the leaf and air-dried. The leaf was left to stand in the thermostatic chamber (25 ± 2 °C, 16L, 8D). After 2 d, the mortality from the formulation of the sample against the two-spotted spider mite was assessed by comparing it with that without the sample.

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References

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