Synthesis of Analogs of Pestalotin

Yasuo KIMURA and Saburo TAMURA

Department of Agricultural Chemistry,
The University of Tokyo,
Bunkyo-ku, Tokyo

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Pestalotin (I), 6-(1'-hydroxypent-1'-yl)-4-methoxy-5,6-dihydro- α -pyrone, was first isolated in 1971 by the present authors¹⁾ as a gibberellin synergist from *Pestalotia cryptomeriaeicola*, a phytopathogenic fungus. Subsequently, Ellestad *et al.*²⁾ obtained the same compound* (designated as LL-P880a) from culture filtrate of an unidentified *Penicillium* sp. (P880) in their program seeking pharmacologically active substances.

In an attempt to obtain new plant growth regulators, we synthesized several compounds containing 4-methoxy-5,6-dihydro- α -pyrone ring. The general procedure for the preparation is illustrated in Fig. 1.

FIG. 1.

* We confirmed the identity of LL-P880a with pestalotin by mixed melting point and spectral measurements. Further, asymmetric synthesis of pestalotin** determined the S configuration at C-1' and C-6.

** Private communication from Dr. Seebach.

Ethyl acetoacetate was condensed with an equimolar amount of trimethyl orthoformate in the presence of a small amount of sulfuric acid to give ethyl β -methoxycrotonate³⁾ (VII), bp 188~190°C, M^+ 144. Treatment of VII with N-bromosuccinimide in refluxing carbon tetrachloride yielded ethyl γ -bromo- β -methoxycrotonate⁴⁾ (VIII), bp 115°C (18 mmHg).

A mixture of VIII (2.2 g), hexen-2-ol-1 (1.0 g), activated zinc dust (0.6 g), tetrahydrofuran (16 ml) and ether (4 ml) was heated under reflux for 6 hr. After cooling to room temperature, the mixture was poured into saturated ammonium chloride solution and extracted repeatedly with ethyl acetate. The combined extracts were washed with water and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was applied to silica gel column chromatography. The column was eluted with benzene and benzene-ethyl acetate mixtures increasing the content of ethyl acetate. An eluate with 95% benzene afforded crude 6-(1'-penten-1'-yl)-4-methoxy-5,6-dihydro- α -pyrone (III). Yield 25%. bp 100~117°C (2 mmHg). IR $\nu_{\text{max}}^{\text{F11m}}$: 1710, 1625. MS (molecular ion peak), m/e : 196. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.91 (3H, t), 1.36 (4H, m), 2.04 (1H, m), 2.51 (1H, m), 3.77 (3H, s), 4.83 (1H, m), 5.15 (1H, m), 5.70 (2H, m).

Then, III (2.8 g) was epoxidized with *m*-chloroperbenzoic acid (2.5 g) in dichloromethane (20 ml) at room temperature for 2 days to give IV. The crude product was applied onto a silica gel column and eluted as in the case of III. Elution with a mixture of benzene-ethyl acetate (92:8) afforded crystals, which were further purified by thin layer chromatography using silica gel GF₂₅₄ and benzene-ethyl acetate (7:3). *Rf* value on the chromatogram was 0.42. Yield 25%. mp 56°C. IR $\nu_{\text{max}}^{\text{Nujol}}$: 1720, 1625. MS (molecular ion peak), m/e : 212. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.98 (3H, t), 1.35 (2H, m), 1.54 (2H, m), 2.53 (1H, m), 2.96 (1H, d), 3.30 (1H, m), 3.76 (3H, s), 4.20 (2H, m), 5.15 (1H, s).

Compound II was prepared by the reaction of VIII with caproic aldehyde. Liquid. IR $\nu_{\text{max}}^{\text{F11m}}$: 1733, 1625. MS (molecular ion peak), m/e : 196. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 0.89 (3H, t), 1.31 (8H, m), 2.38 (1H, m), 2.60 (1H, m), 3.73 (3H, s), 4.19 (1H, m), 5.12 (1H, d).

Similarly, compound V was obtained from perillaldehyde and VIII in an yield of 15%. bp 150°C (2 mmHg). IR $\nu_{\text{max}}^{\text{F11m}}$: 1712, 1690 (sh), 1640 (sh), 1626. MS (molecular ion peak), m/e : 248. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 1.71 (3H, s), 2.10 (9H, br), 3.75 (3H, s), 4.70 (3H, br), 5.14 (1H, d), 5.85 (1H, br).

Kawain (VI) was synthesized from III and *trans*-cinnamic acid by the same procedure. mp 146~147°C (lit.⁵⁾ 146~147°C). IR $\nu_{\text{max}}^{\text{Nujol}}$: 1700, 1625. MS (molecular ion peak), m/e : 230. NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CDCl}_3}$: 2.56 (2H, m), 3.71 (3H, s), 5.0 (1H, m), 5.15 (1H, s), 6.21 (1H, q), 6.70 (1H, d).

Contrary to our expectation, compounds, II~VI, did not show any synergistic activity with gibberellin A₃, when they were applied to rice seedlings.

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