A Novel Synthesis of 3-Substituted Furans: Synthesis of Perillen and Dendrolasin

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Received July 10, 1974

A novel synthetic method of 3-substituted furans was developed and syntheses of perillen and dendrolasin are described.

A number of 3-substituted furans are known in terpenoid field and some of them have been synthesized. In the earlier syntheses, the furan moieties originated from inaccessible 3-furoic acid or 3-furyl lithium. Recently two groups reported the syntheses of these type compounds from nonfuranoid precursors.^{1,2)}

We attempted to establish an alternative construction of 3-substituted furans and devised introductions of the substituents by nucleophilic attacks of the appropriate reagents, *e.g.*, Grignard, to carbonylated four-carbon unit, 5-ethoxytetrahydrofuran-3-one (VI).

In this paper we would describe the syntheses of perillen (I)³⁾ and dendrolasin (II).⁴⁾

The starting 1,1-diethoxybut-3-ene (III)⁵⁾ was readily available as a dimer of ethyl vinyl ether. Oxidation of III with aqueous potassium permanganate gave diol (IV). This was stirred with cation-exchange resin (Amberlite IR 120 H⁺) in ether to afford quantitatively

cyclized product (V), which consisted of two components detectable with gas chromatography. Since GC-connected mass spectra of these two gave same fragmentation patterns, it seemed that they were *cis-trans* isomers at C₃ and C₆ positions.

An attempt to separate them from each other by distillation was unsuccessful.

In order to obtain 3-oxocompound (VI), a number of conditions of oxidation were examined but most of them, except ruthenium tetroxide oxidation, gave little or no desired product.

The oxidized product (VI) was prepared in moderate yield (55.8%) by reaction of V with excess ruthenium tetroxide in carbon tetrachloride. However, on a large scale preparation of VI, Parikh and Jones' procedure,⁶⁾ using only a small quantity of costly ruthenium dioxide, was employed. The IR, NMR, MS and analytical data of VI indicated the structure shown.

Perillen (I) and dendrolasin (II) were typical naturally occurring 3-substituted furans. The former was isolated from the essential oil of the leaves of *Perilla citriodora* Makino³⁾ and the latter initially from the ant *Lasius (Dendrolasius) fuliginosus* Latr.⁴⁾

Although these had already been synthesized by some groups,^{1,2,7)} we were interested in syntheses of them to confirm an availability of the potential furan precursor (VI).

The introduction of 3-substituents were carried out by Grignard reactions with known

4-methylpent-3-enyl magnesium bromide and 4,8-dimethylnona-3,7-dienyl magnesium bromide,⁸⁾ respectively.

The resulting crude products of these reactions were heated in toluene with the catalytic amounts of *p*-toluenesulfonic acid to eliminate water and ethanol.

Perillen (I) and dendrolasin (II) were obtained as the predominant products after chromatography and the yields of them, based on VI, were 37% and 28.3%, respectively. Spectral data of the synthesized products were identical with those of published ones.^{4,9)}

As described above, our attempts to construct 3-substituted furans were successful. Thus many other compounds of this type should be possible to be prepared by this method.

EXPERIMENTAL¹⁰⁾

4,4-Diethoxybutan-1,2-diol (IV)

III (57.6 g) was stirred with 480 ml of water, cooling on an ice-methanol bath. To the mixture was added a solution of 64 g of potassium permanganate in 1.2 liters of water during 1 hr at 5°C with stirring. After completion of the addition, the reaction mixture was allowed to stand at room temperature for 2 hr and then heated on a steam bath for 0.5 hr. The hot mixture was filtered to remove the formed manganese dioxide, which was then washed with hot water.

After cooling, the combined filtrates were saturated with potassium carbonate and extracted with ether. The ethereal extract was washed with saturated sodium chloride solution and dried over anhydrous potassium carbonate. Removal of the solvent, followed by distillation of the residual oil, gave 44.0 g (61.8%) of diol (IV). bp 122~3°C/4 mmHg. n_D^{26} 1.4402. IR $\nu_{\max}$ (film): 3400, 1050 cm⁻¹.

5-Ethoxytetrahydrofuran-3-ol (V)

An ethereal solution of IV (45.0 g in 450 ml) was stirred at room temperature with 15 g of Amberlite IR 120 H⁺, previously washed with distilled water, ethanol and ether. The stirring was continued for 1.5 hr and the exchange resin was filtered off. The filtrate was concentrated *in vacuo* and trace amounts of contaminants (ether and ethanol) were minimized by further evacuating with vacuum pump (6 mmHg) at room temperature. The residue (32.5 g, 98.5% yield) was a mixture of two components detectable with gas chromatography and GC-MS data showed them

to be diastereomers because of their fragmentation patterns being same. The mixture was used for the next reaction without further purification. IR $\nu_{\max}$ 3400 cm⁻¹. Anal. Found: C, 54.49; H, 9.09. Calcd. for C₆H₁₂O₃: C, 54.53; H, 9.15%.

Principal peaks of MS were at *m/e* 102, 87 (100), 75, 73, 69, 58, 57, 47, 45, 43.

Ruthenium tetroxide oxidation of V, 5-ethoxytetrahydrofuran-3-one (VI)

Method (A). Ruthenium dioxide (5 g), supplied by Engelhard Industries, was stirred in 300 ml of carbon tetrachloride and a solution of 50 g of sodium metaperiodate in 500 ml of water was added to the suspension with stirring at 10~15°C. The stirring was continued for 2 hr to dissolve black dioxide completely.

The yellow carbon tetrachloride layer was separated and cooled on ice-methanol bath. Then a solution of 4.0 g of V in 100 ml of carbon tetrachloride was added with stirring to the yellow solution at -7~-10°C and the stirring was continued for 1 hr. Isopropyl alcohol (1 ml) was added to destroy the excess oxidant and the mixture was filtered with suction to remove black oxide.

The filtrate was washed successively with 5% sodium thiosulfate, water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the solvent, distillation of the residue gave 2.2 g (55.8%) of VI. bp 72°C/20 mmHg. n_D^{16} 1.4331. IR $\nu_{\max}$ (film): 3520, 1760, 1340, 1260, 1160, 1100, 1060, 1040, 900 cm⁻¹. NMR δ_{TMS}^{14} : 1.20 (3H, t, *J*=7 Hz), 2.24 (1H, double d, *J*=-16, 1.5 Hz), 2.54 (1H, double d, *J*=-16, 5 Hz), 3.75 (2H, s), 5.36 (1H, double d, *J*=1.5, 5 Hz). Anal. Found: C, 55.39; H, 7.85. Calcd. for C₆H₁₀O₃: C, 55.39; H, 7.75%. MS *m/e*: 130 (M⁺, 67), 85 (79), 72 (100), 57 (51), 43 (58).

Method (B). A solution of 32.5 g of V in 1.3 liters of carbon tetrachloride was stirred with 1 g of ruthenium dioxide and a solution of 80 g of sodium metaperiodate in 1.2 liters of water was added dropwise to the mixture during 1.5 hr at room temperature with vigorous stirring.

The pH of the reaction mixture was controlled between 6 to 7 by periodic addition of dilute aqueous sodium bicarbonate solution.

After the completion of the addition the mixture was stirred for 1 hr at room temperature. An additional amount (15 g) of aqueous sodium metaperiodate solution (200 ml) was added to the mixture and the stirring was continued for further 45 min. Isopropyl alcohol (20 ml) was then added to destroy the excess oxidizing agent and black dioxide was removed by filtration through celite. The carbon tetrachloride layer was separated and the aqueous layer was extracted twice

with 300 ml of carbon tetrachloride. The combined organic layer was washed successively with water, 5% sodium thiosulfate, water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo*, followed by distillation of the residual oil, gave 14.1 g (44.1%) of VI.

Perillen (I)

A solution of 13.0 g of VI in 80 ml of dry ether was added dropwise to an ethereal solution of 4-methylpent-3-enyl magnesium bromide, prepared from 2.9 g of magnesium and 19.5 g of 4-methylpent-3-enyl bromide in 100 ml of dry ether,⁶¹ at $-6 \sim -0^\circ\text{C}$ with stirring.

The mixture was left to stand overnight at room temperature and poured into ice and aqueous ammonium chloride solution. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with saturated ammonium chloride and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 15.2 g of oily product.

The crude product (7.2 g) and a trace amount of *p*-toluenesulfonic acid was heated in 80 ml of toluene under reflux for 5 hr with a water separator. After cooling, the reaction mixture was washed with saturated sodium bicarbonate, water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on 100 g of silica gel. Elution with *n*-hexane afforded 2.9 g (37%) of perillen (I). bp $81^\circ\text{C}/20\text{ mmHg}$ (lit. $185 \sim 186^\circ\text{C}$).³¹ n_D^{21} 1.4723 (lit. n_D^{21} 1.4705).³¹ IR ν_{max} (film): 3130, 1670, 1565, 1500, 1160, 1025, 875, 780 cm^{-1} . NMR $\delta_{\text{TMS}}^{\text{CCl}_4}$: 1.58 (3H, s), 1.68 (3H, s), 5.11 (1H, m), 6.18 (1H, m), 7.12 (1H, m), 7.24 (1H, m). MS *m/e*: 150 (M^+ , 52), 135 (8), 94 (6), 82 (26), 81 (62), 69 (100), 53 (26), 41 (79), 39 (17).

Dendrolasin (II)

A solution of 12.7 g of VI in 40 ml of dry ether was added dropwise to an ethereal solution of 4,8-dimethylnona-3,7-dienyl magnesium bromide, prepared from 2.7 g of magnesium and 25.5 g of 4,8-dimethylnona-3,7-dienyl bromide in 80 ml of dry ether,⁸¹ at 0°C with stirring.

The mixture was allowed to stand overnight at room temperature and poured into ice and aqueous ammonium chloride solution. The ethereal layer was separated and the aqueous layer was extracted with ether.

The combined extracts were washed with saturated

ammonium chloride and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* gave 24.1 g of oily product.

The crude product (8.0 g) and a trace amount of *p*-toluenesulfonic acid was heated in 300 ml of toluene under reflux for 2.5 hr with a water separator. After cooling, the mixture was washed with saturated sodium bicarbonate, water and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on 100 g of silica gel. Elution with *n*-hexane afforded 2.0 g (28.3%) of dendrolasin (II). bp $152^\circ\text{C}/18\text{ mmHg}$ (lit. $148 \sim 150^\circ\text{C}/16\text{ mmHg}$).⁴¹ n_D^{18} 1.4891 (lit. n_D^{20} 1.486).⁴¹ IR ν_{max} (film): 3100, 1660, 1560, 1500, 1165, 1065, 1025, 875, 780 cm^{-1} . NMR $\delta_{\text{TMS}}^{\text{CCl}_4}$: 1.59 (6H, s), 1.68 (3H, s), 5.09 (2H, m), 6.19 (1H, m), 7.14 (1H, m), 7.25 (1H, m). MS *m/e*: 218 (M^+ , 2), 203 (4), 175 (6), 136 (6), 123 (5), 95 (8), 82 (14), 81 (58), 69 (100), 53 (15), 41 (42), 39 (9).

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- 10) NMR spectra were measured with a Varian HA 100 D spectrometer. Mass spectra were recorded on a Japan Electron Optics Lab. JMS O1 SG spectrometer at 75 eV.