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Synthesis of *p*-Coumar-, Coniferyl- and Sinap Aldehydes*

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Abstract——*p*-Coumar-, coniferyl- and sinap aldehydes were synthesized in good yields by new two synthetic methods. 1) The aldehydes were prepared by a two-carbon homologation of *p*-hydroxybenzaldehyde, vanillin and syringaldehyde with 2, 4, 4, 6-tetramethyl-5, 6-dihydro-1, 3-oxazine in the presence of *n*-butyllithium in anhydrous tetrahydrofurane at −77°C. 2) The aldehydes were also prepared by reduction of the corresponding *p*-hydroxycinnamic acid chlorides with lithium tri-*t*-butoxyaluminohydride in anhydrous diglyme at −77°C.

Introduction

The occurrence of lignin in woody plants has long been observed by botanists and wood chemists using phloroglucinol-HCl color reaction[1]. The red color formed in this reaction with plant materials is attributed to *p*-hydroxycinnamyl aldehyde groups of lignin molecules[2], and in fact coniferyl aldehyde has been obtained in the hydrolysis products of lignin[3].

On the other hand, *p*-hydroxycinnamyl aldehydes, especially coniferyl aldehyde, were detected in the extracts of cambial zone and woods[4~7], and tracer experiment suggested that coniferyl aldehyde was an intermediate in reduction of ferulic acid to coniferyl alcohol[8].

ZENK *et al.* recently established the enzymic mechanism of formation of coniferyl aldehyde from ferulic acid[9]. The present authors also reported that ferulic and sinapic acids were reduced to the corresponding aldehydes which were further reduced to the alcohols in several plants[10]. Thus the *p*-hydroxycinnamyl aldehydes are believed to be obligatory intermediates in lignin biosynthesis.

While synthetic methods of the aldehydes have been reported[11~14], their yields are very low. In the present investigation, two synthetic methods have been applied for preparation of *p*-hydroxycinnamyl aldehydes, 1) a two-carbon homologation of *p*-hydroxybenzaldehydes by hydrolysis of a substituted six-membered heterocyclic ring, 2) reduction of *p*-hydroxycinnamic acid chlorides with lithium tri-*t*-butoxyaluminohydride.

Experimental

1. Two-carbon homologation of *p*-hydroxybenzaldehydes

2, 4, 4, 6-Tetramethyl-5, 6-dihydro-1, 3-oxazine (2-methyloxazine) (I)——This reagent was prepared from acetonitrile and 2-methyl-2, 4-pentanediol by the method of MEYERS *et al.*[15] NMR (CCl_4) δ (ppm) : 1.07 (6H, s, C_4-$(CH_3)_2$), 1.19 (3H, d, J***=6.0, C_6-CH_3), 1.76 (3H, s, C_2-CH_3), 4.03 (1H, m, C_6-H).

Tetrahydropyranyl ether (THP) derivatives of p-hydroxybenzaldehydes (IIa, IIb, IIc)——The THP derivatives were prepared by the usual method. A mixture of each of *p*-hydroxybenzaldehydes (25–30 m moles) and 2, 3-dihydropyrane (50–60 m moles) containing *DL*-camphor-10-sul-

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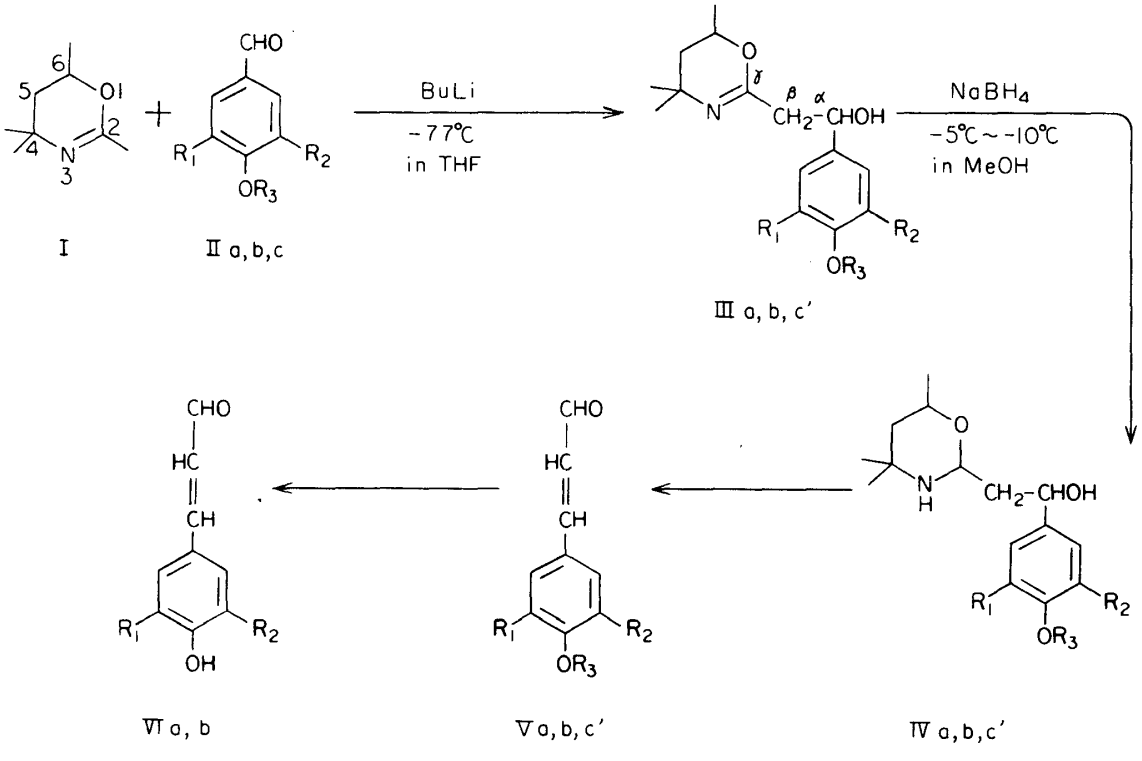
*** J : Coupling constant (Hz).

fonic acid (2–4 mg) was magnetically stirred for 1 hr (*p*-hydroxybenzaldehyde), 3 hr (vanillin) and/or 6 hr (syringaldehyde) at room temperature avoiding any moisture, respectively. The THP derivatives of aldehydes were obtained quantitatively.

2-Substituted 4, 4, 6-trimethyl-5, 6-dihydro-1, 3-oxazines (IIIa, IIIb, IIIc′)——A 100 ml flask equipped with a magnetic stirring bar and a rubber septum was evacuated and flushed with dry nitrogen gas by syringe needles through the rubber septum. Anhydrous tetrahydrofurane (6 ml) and 776 mg (5.5 m moles) of 2-methyloxazine were added to the flask by a syringe through the septum. The stirred solution was cooled to −77°C with a dry ice acetone bath and 4.3 ml (6.0 m moles, 1.39 M) of *n*-butyllithium in hexane was added over a period of 30 min. Stirring was continued for 30 min, in which yellow precipitates of the lithio anion of 2-methyloxazine were formed. After additional 1 hr stirring, a THP derivative of aldehyde (5.0 m moles) dissolved in 6 ml of anhydrous tetrahydrofurane was added to the mixture over a period of 15 min and the solution was stirred for further 15 min. The reaction mixture was allowed to slowly warm up to room temperature, in which the yellow precipitates disappeared. The mixture was poured into 30 ml of cooled water and it was extracted with ether (20 ml×4). The ether extracts were washed with saturated NaCl solution and dried over anhydrous K_2CO_3. The solvent was evaporated and a 2-substituted dihydro-1, 3-oxazine was obtained (90–92 % yields). The data of NMR and MS of the compounds obtained were in good agreement with the structures of IIIa, IIIb and IIIc′ in Scheme 1.

Compound IIIa, NMR ($CDCl_3$) δ (ppm) : 1.24 (3H, d, J=6.4, C_6-CH_3), 2.40 (1H, d, J=6.6,



	R_1	R_2	R_3
a	H	H	THP*
b	H	OMe	THP
c	OMe	OMe	THP
c′	OMe	OMe	H

* THP ; tetrahydropyranyl

Scheme 1. Synthetic route of *p*-hydroxycinnamyl aldehydes by a two-carbon homologation of *p*-hydroxybenzaldehydes.

C_β-H), 2.44 (1H, d, J=6.6, C_β-H), 4.08 (1H, m, C_6-H), 4.96 (1H, t, J=6.6, C_α-H), 5.42 (1H, broad s, C_α-OH), 7.03 (2H, d, J=8.8, Ar ; Aromatic), 7.33 (2H, d, J=8.8, Ar). MS *m/e*: 347 (M^+), 263 (M^+–DHP, DHP ; 2, 3-dihydropyrane), 245 (263–H_2O), 230 (245–$CH_3\cdot$), 147 (Ⓗ*—CH=CH—C≡O^+), 141 (oxazine ion $CH(CH_3)—CH_2—C(CH_3)_2—NH—C(=CH_2)—\overline{O}|^{\cdot+}$), 123 (Ⓗ—CH=$O^+$H), 122 (Ⓗ—CH=$O^{\cdot+}$), 121 (Ⓗ—C≡$O^+$), 99, 85 (THP ion $CH=O^+\text{-}(\text{-}CH_2\text{-})_3\text{-}CH_2$, base ion), 43.

Compound IIIb, NMR ($CDCl_3$) δ (ppm) : 2.42 (2H, d, J=6.4, C_β-H_2), 3.87 (3H, s, Ar-OCH_3), 4.08 (1H, m, C_6-H), 4.96 (1H, t, J=6.4, C_α-H), 5.39 (1H, broad s, C_α-OH), 6.98 (3H, m, Ar). MS *m/e*: 377 (M^+), 293 (M^+–DHP), 275 (293–H_2O), 260 (275–$CH_3\cdot$), 177 (Ⓖ*—CH=CH—C≡O^+), 153 (Ⓖ—CH=O^+H), 152 (Ⓖ—CH=$O^{\cdot+}$), 151 (Ⓖ—C≡O^+), 141 (oxazine ion), 99, 85 (THP ion, base ion), 43.

Compound IIIc', NMR ($CDCl_3$) δ (ppm) : 1.27 (3H, d, J=6.3, C_6-CH_3), 2.43 (1H, d, J=6.0, C_β-H), 2.47 (1H, d, J=6.0, C_β-H), 3.84 (6H, s, Ar-$(OCH_3)_2$), 4.23 (1H, m, C_6-H), 4.93 (1H, t, J=6.0, C_α-H), 5.38 (1H, broad s, C_α-OH), 6.62 (2H, s, Ar). MS *m/e*: 323 (M^+), 305 (M^+–H_2O), 290 (305–$CH_3\cdot$), 207 (Ⓢ*—CH=CH—C≡O^+), 183 (Ⓢ—CH=O^+H), 182 (Ⓢ—CH=$O^{\cdot+}$, base ion), 181 (Ⓢ—C≡O^+), 141 (oxazine ion), 99, 43.

2-Substituted 4, 4, 6-trimethyl-2, 3, 5, 6-tetrahydro-1, 3-oxazines (IVa, IVb, IVc')——An aliquot (2 m moles) of a crude dihydrooxazine was dissolved in a minimum volume of methanol, and the solution was cooled to $-5°\sim-10°C$ with salt and ice. Sodium borohydride (2 m moles) was added to the solution which was stirred for 30 min. The contents were poured into 20 ml of NaCl saturated water and the aqueous solution was extracted with ether (15 ml×4). The combined ether extracts were dried over anhydrous K_2CO_3, the ether was removed, and the crude tetrahydrooxazine was obtained (about 90 % yields).

p-Hydroxycinnamyl aldehydes (VIa, VIb, Vc')——The crude tetrahydro-1, 3-oxazine obtained in the preceeding experiment was dissolved in 1 ml of ethanol and then 1 ml of ammonium chloride solution (6N) was added to the mixture, which was subsequently acidified (pH 5-6) with oxalic acid. The mixture was stirred for 24 hr at room temperature, in which the oxazine rings of the compounds IVa, IVb, IVc' were hydrolyzed. All of *p*-coumar aldehyde and a part of coniferyl aldehyde were obtained as THP derivatives (Va, Vb), but in the case of IVc' sinapaldehyde was directly obtained, since THP group had been removed during homologation reaction. To obtain free aldehydes of the two formers, ethanol solution (1 ml) of *DL*-camphor-10-sulfonic acid (2 mg) was added to the mixture, which was stirred for additional 1-2 hr. The mixture was poured into 20 ml of NaCl saturated water and it was extracted with ether (15 ml×4). The ether extracts were dried over anhydrous Na_2SO_4 and the ether was removed. The aldehydes were obtained from dihydro-1, 3-oxazines (IIIa, IIIb, and IIIc') in 67-73 % yields. The following analytical data of the aldehydes were completely identical with those of authentic compounds.

p-Coumar aldehyde VIa, Overall yield : 63 %. m.p. 134°C (lif.[11] 134°C). Red coloration with phloroglucinol-HCl. IR ν (KBr) cm^{-1} : 1647 (—CHO), 970 (C=C, trans), 810 (Ar). NMR (CD_3COCD_3) δ (ppm) : 6.56 (1H, dd, J=16.0, 8.0, C_β-H), 6.83 (2H, d, J=8.8, Ar), 7.48 (2H, d, J=8.8, Ar), 7.53 (1H, d, J=16.0, C_α-H), 9.48 (1H, d, J=8.0, C_γ-H). UV λ_{max}^{EtOH} mμ (ε) : 324-325 (30 000). MS *m/e*: 148 (M^+, base ion), 147 (M^+—H•), 131, 120, 119 (147–CO), 91 (119–CO), 65 (91–(CH≡CH)). Metastable peaks : 146.01 (148→147), 96.33 (147→119), 69.59 (119→91), 46.43 (91→65).

Coniferyl aldehyde VIb, Overall yield : 64 %. m.p. 80-82°C (lif.[12] 82.5°C). Red purple coloration with phloroglucinol-HCl. IR ν (KBr) cm^{-1} : 2850 (Ar-OCH_3), 1682 (—CHO), 1227 (Ar-OCH_3), 1028 (Ar-OCH_3), 967 (C=C, trans), 883 (Ar), 813 (Ar). NMR ($CDCl_3$) δ (ppm) : 3.92 (3H, s, Ar-OCH_3), 6.56 (1H, dd, J=16.0, 7.8, C_β-H), 6.88-7.16 (3H, m, Ar), 7.38 (1H, d, J=16.0, C_α-H), 9.62 (1H, d, J=7.8, C_γ-H). UV λ_{max}^{EtOH} mμ (ε) : 340 (23 800). MS *m/e*: 178 (M^+, base ion), 177 (M^+–H•), 163 (M^+–$CH_3\cdot$), 147 (177–CH_2O), 135 (163–CO), 119 (147–CO), 107, Metastable peaks : 176.01 (178→177), 122.08 (177→147), 96.33 (147→119).

* Abbreviations : Ⓗ, *p*-Hydroxyphenyl ; Ⓖ, Guaiacyl, (3-Methoxy-4-hydroxyphenyl) ; Ⓢ, Syringyl, (3, 5-Dimethoxy-4-hydroxyphenyl).

Sinapaldehyde Vc', Overall yield : 62 %. m.p. 106–107°C (lif.[14] 109°C). Purple coloration with phloroglucinol-HCl. IR ν (KBr) cm^{-1} : 2854 (Ar-OCH_3), 1660 (—CHO), 1259 (Ar-OCH_3), 975 (C=C, trans), 810 (Ar). NMR ($CDCl_3$) δ (ppm) : 3.94 (6H, s, Ar-$(OCH_3)_2$), 6.59 (1H, dd, J=16.0, 7.8, C_β-H), 6.82 (2H, s, Ar), 7.40 (1H, d, J=16.0, C_α-H), 9.67 (1H, d, J=7.8, C_γ-H). UV λ_{max}^{EtOH} mμ (ε) : 345 (24 300). MS *m/e* : 208 (M^+, base ion), 207 (M^+-H·), 193 (M^+-CH_3·), 180, 177 (207-CH_2O), 165 (193-CO), 137, Metastable peaks : 206.00 (208→207), 151.35 (207→177).

Method of analysis——HITACHI model 124 double beam spectrometer and JASCO model IR-S were used for UV and IR spectra, respectively. NMR spectra were taken by the use of R22 HITACHI high resolution NMR spectrometer (90 MHz) with TMS internal standard. Mass spectrometry was conducted by the use of SHIMAZU-LKB 9000 gas chromatograph-mass spectrometer.

2. Reduction of *p*-hydroxycinnamic acid chlorides with lithium tri-*t*-butoxyaluminohydride

Lithium tri-t-butoxyaluminohydride——This reagent was prepared by the method of BROWN *et al.*[16]

Acetyl p-hydroxycinnamic acid chlorides——*p*-Coumaric, ferulic and sinapic acids were synthesized by condensation of the corresponding *p*-hydroxybenzaldehydes and malonic acid[17], and these acids were subsequently acetylated in anhydrous acetic acid and pyridine (yields of the products for 2 steps ; 81–85 %). The acetyl *p*-hydroxycinnamic acids were converted to their acid chlorides in refluxing with thionyl chloride for 3 hr, and the products were recrystallized from xylene before use (about 90 % yields).

p-Hydroxycinnamyl aldehydes——One of the *p*-hydroxycinnamic acid chlorides (7.0 m moles) was dissolved in 40 ml of anhydrous diglyme in a three-necked flask equipped with a stirring bar, a dropping funnel, a low temperature thermometer and a gas inlet glass tube. The flask was flushed with dry nitrogen and cooled to about −77°C in a dry ice acetone bath. Lithium tri-*t*-butoxyaluminohydride (7.0 m moles) in anhydrous diglyme (20 ml) was added over a period of 1 hr with stirring, avoiding any major rise in temperature. The cooling bath was then removed and the flask was allowed to warm up to room temperature over a period of 1 hr. The contents were then poured into 100 ml of water, which was cooled and weakly acidified with dry ice, and extracted with ether (30 ml×4). The extracts were dried over anhydrous Na_2SO_4 and the solvent was evaported. The oily acetyl *p*-hydroxycinnamyl aldehyde was kept in a refrigerator, and the crude crystal obtained was washed with *n*-hexane. The acetyl aldehyde was deacetylated with sodium methoxide in the conventional way[14]. Recrystallization was performed with benzene. A small amount of *p*-hydroxycinnamyl alcohols, which were identified by GC-MS, was detected in the mother liquor. The total yields of these aldehydes based on the corresponding *p*-hydroxybenzaldehydes were as follows ; *p*-coumar aldehyde, 30 % ; coniferyl aldehyde, 32 % ; sinapaldehyde, 34 %. The analytical data of three aldehydes, which were obtained by IR, NMR, UV and mass spectrometry, were completely identical with those described above.

Results and Discussion

In earlier investigations, PAULY and WÄSCHER[11] synthesized *p*-coumar and coniferyl aldehydes by aldol condensation of methoxymethyl ether derivatives of *p*-hydroxybenzaldehydes with acetaldehyde. In their method, α, β-unsaturated aldehydes were formed by the two-carbon homologation of *p*-hydroxybenzaldehydes. The yields, however, were very low (*p*-coumar aldehyde, 26 % ; coniferyl aldehyde, 18 %) because of the alkaline condition at high temperature and the prolonged reaction time. In addition to the condensation reaction, the step of synthesis of methoxymethyl ether derivatives of *p*-hydroxybenzaldehydes also caused a decrease of overall yields of the end products (*p*-coumar aldehyde <12 %, coniferyl aldehyde <10 %). Although they prepared coniferyl aldehyde in 24 % overall yield by a modified method[12], the yield of sinapaldehyde was only 12 %[13].

FREUDENBERG and HÜBNER[14] obtained acetyl sinapaldehyde from acetyl sinapic acid chloride in 36 % yield by the ROSENMUND reduction, and the overall yield of sinapaldehyde based on syringaldehyde was only 22 %. The present authors prepared coniferyl aldehyde in a similar yield by this method. The low yield of the products was due to a strong acid condition and high temperature. Furthermore, several by-products formed during the reduction made difficult isolation and purification of the aldehydes. In the ROSENMUND reduction it is difficult to reproduce the precise poisoning of catalyst, that is, reduction of acid chloride does not proceed in the presence of excess catalyst poison, but the chloride is overreduced to the alcohol in the absence of the poison.

Thus, it is desired that reduction is carried out in neutral condition at low temperature with a selective reducing reagent. It has recently been established that lithium tri-*t*-butoxyaluminohydride is very effective for reduction of acid chlorides to the corresponding aldehydes[18]. This reagent possesses the following advantages: 1) it is a far milder reducing agents than lithium aluminum hydride, 2) the yield of reduced product is favored in low temperature, 3) the procedure is exceedingly simple and then it provides a valuable synthetic route of aldehydes. In this experiment, the *p*-hydroxycinnamic acid chlorides were reduced to the corresponding aldehydes with lithium tri-*t*-butoxyaluminohydride in 45–50 % yields, which were higher than those in the ROSENMUND reduction by 10–15 %. As the synthetic routes other than the reduction step of acid chlorides are common to the both methods, the overall yields of the aldehydes increased from 22 % to 30–34 %. Since it was reported that cinnamic acid chloride gave cinnamaldehyde in the yield of 50 %, the overall yields of *p*-hydroxycinnamyl aldehydes were regarded to be reasonable. The *p*-hydroxycinnamyl alcohols detected in the mother liquors of the corresponding aldehydes might be due to the occurrence of minor amounts of lithium aluminum hydride, which is the parent compound of lithium tri-*t*-butoxyaluminohydride.

As one of the synthetic methods of aldehydes, the hydrolysis of six-membered heterocyclic rings was reported[19]. This synthesis is due to the fact that dihydro-1, 3-oxazine is converted into anion and that the reaction of the anion with a carbonyl compound results in the desired aldehyde after hydrolysis. The synthetic method has the following advantages: 1) 2-methyl dihydro-1, 3-oxazine is readily prepared as starting material, 2) lithio carbanion of 2-methyl oxazine, generated by the use of *n*-butyllithium, is very stable in low temperature, 3) the reaction of the carbanion with electrophiles is rapid and irreversible, and then alkylation of oxazine ring proceeds quantitatively. On the other hand, since all oxazine derivatives are oily and difficult to be isolated and purified, crude products are forced to be subjected to subsequent reactions without purification. Moreover phenolic hydroxyl group inhibited the formation of lithio anion of 2-methyloxazine, and then the hydroxyl group was protected as tetrahydropyranyl ether with 2, 3-dihydropyrane. The dihydropyrane easily reacted with phenols by the catalytic action of acids (*DL*-camphor-10-sulfonic acid or *p*-toluenesulfonic acid), affording the THP derivatives of *p*-hydroxybenzaldehydes. The derivatives were basic and stable under the condition, where oxazine derivatives were prepared and reduced with sodium borohydride. In spite of quantitative conversion of *p*-hydroxybenzaldehydes to their oxazine derivatives, overall yields of *p*-hydroxycinnamyl aldehydes were limited to about 60 %. This may be ascribed partly to overreduction of the dihydro-1, 3-oxazines to open-chain amino alcohols through tetrahydrooxazines during borohydride reduction and to prolonged standing in the cleavage of the tetrahydrooxazines to the aldehydes.

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