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Behaviour of Salicylaldehyde and Some of Its Derivatives in the Biginelli Reaction for the Preparation of Aryl Tetrahydropyrimidines

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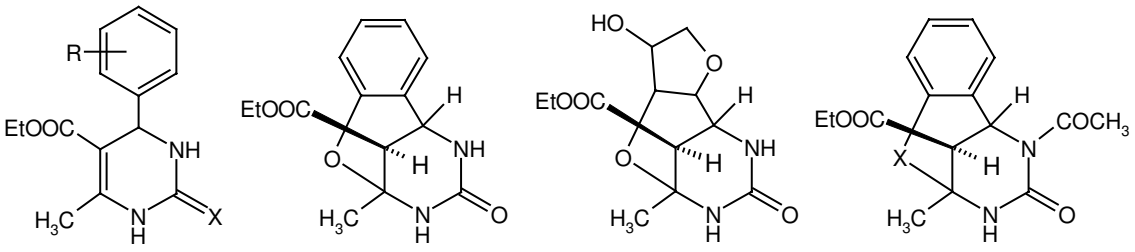
Salicylaldehyde and some of its derivatives react with urea (or thiourea) and ethyl acetoacetate (the Biginelli reaction) to give products that depend on the type of the substituent in the *ortho*-position to the hydroxyl group. Aldehydes having oxygen-bearing substituents *ortho* to the hydroxyl group (e.g., OCH_3, NO_2, COOH) undergo chelation with the hydroxyl proton and lead to 4-aryl-6-methyl-4-aryl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-ethyl carboxylate (the classical Biginelli product). Compounds not having such a property give oxacyclic products formed by addition of the hydroxyl proton to the C5-C6 double bond of the pyrimidine ring. This study also includes compounds having an amino group instead of the hydroxyl one.

Key Words: Salicylaldehyde derivatives, Biginelli reaction, Michael addition

Introduction

In the last 2 decades, 5-acyl-4-aryl-1,2,3,4-tetrahydropyrimidines (**I**), known as "Biginelli[1] compounds", have received significant attention due to their wide range of biological activities.[2−8] Many of these compounds are very potent calcium channel blockers and are used in the treatment of cardiovascular disorders.[9−17] In addition, the presence of various interacted functional groups determine their great synthetic potentials.[18]

The steric proximity of the substituent group (e.g., OH, NH, SH) attached to the aromatic nucleus located at the *ortho*-position to the pyrimidine ring in Biginelli compounds and the C6 of the pyrimidine ring may enable the formation of a 6-membered cycle via intramolecular Michael-type addition.

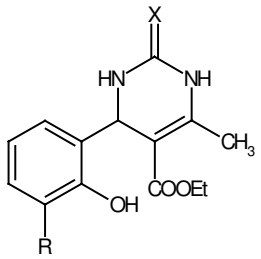


I **II** **III** **IV**

R = substituent(s); X = O,S

There are discrepancies, however, in assigning the product's structures obtained from salicylaldehyde and some of its derivatives. Thus, while some researchers reported that the product obtained from the reaction of salicylaldehyde with urea and ethyl acetoacetate has the classical Biginelli tetrahydropyrimidine structure[4,19,20] (**I,** R=*o*−OH), others[21−24] proved that this reaction gave the oxygen-bridged structure **II**, which was formed by the addition of the phenolic hydroxyl proton to the C6 of the pyrimidine ring. A similar type of addition product was also reported with 4-substituted alkoxy or aryloxy glucosides upon their hydrolysis[25] (as in **III**). Moreover, a general synthetic method for the synthesis of O-, S-, and N-bridged structures has been reported,[22] which was based on the use of acetic anhydride for formation of the bridged rings (as in **IV**).

More recently, Stiasni and co-workers[23] reported that an *ortho*-amino group in the aromatic ring could undergo, under microwave radiation, a Michael-type addition of the amine-proton to the C6 of the pyrimidine ring, giving rise to the NH-bridged structure (**IV**).



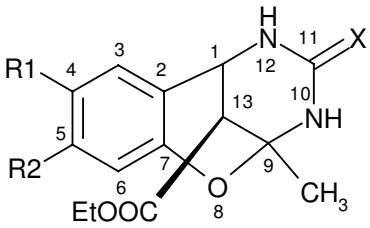
8) R = NO_2, X = O **9**) R = NO_2, X = S; **10**) R = OMe, X = O
11) R = OMe, X = S; **12**) R = COOH, X = O

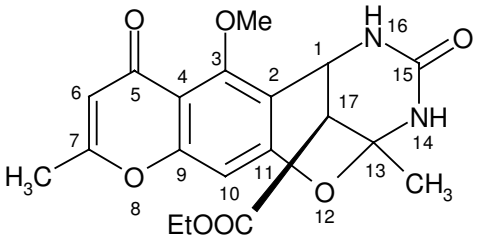
However, none of the publications that mentioned this observation gave reasons or explained on what basis Michael-type addition takes place in such a reaction. In the present work we tried to explore to some extent this behaviour by carrying out the Biginelli reaction using salicylaldehyde and some of its derivatives in addition to other related structures.

Results and Discussion

Salicylaldehyde (**1**), 2,4-dihydroxybenzaldehyde (**2**), 2-hydroxy-5-nitrobenzaldehyde (**3**), 7-hydroxy-5-methoxy-2-methyl-4-oxo-4H-chromene-6-carbaldehyde (**4**), 2-hydroxy-3-nitrobenzaldehyde (**5**), 2-hydroxy-3-methoxybenzaldehyde (**6**), and 3-formyl-2-hydroxybenzoic acid (**7**) were used in this investigation. The Biginelli reaction was undertaken by reacting any of the foregoing aldehydes with urea and ethyl acetoacetate. Thiourea was also used in place of urea in some examples.

The products obtained from the reaction of the compounds **5**, **6**, and **7** with urea (or thiourea) and ethyl acetoacetate were found to have the classical Biginelli structure (**8-12**).





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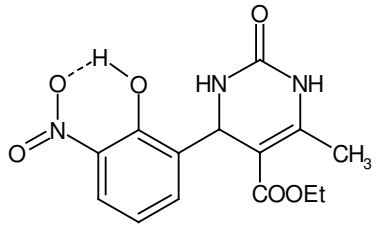
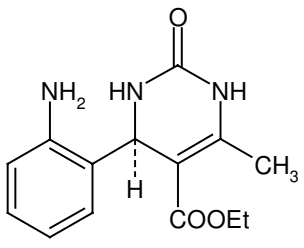
13) $R_1 = R_2 = H$, X = O;
14) $R_1 = R_2 = H$, X =S
15) $R_1 = NO_2$, $R_2 = H$, X =O;
16) $R_1 = H$, $R_2 = OH$, X =O;
17) $R_1 = H$, $R_2 = OH$, X =S

On the other hand, compounds **1**, **2**, **3**, and **4** gave oxygen-bridged products (**13-18**).



The results obtained indicate that the difference in the behaviour of the hydroxyl group may be explained in terms of the electronegativity exerted by the neighbouring group. In the examples given a hydrogen bond between the oxygen atoms of the nitro-, the methoxyl, or the carboxylate groups and the adjacent hydroxyl proton may prevent the simultaneous addition of the hydrogen atom to the C5-C6 double bond of the pyrimidine ring, as shown below:

There may be other factors that enable the hydroxyl-oxygen to combine with the C6 carbon, as for example the creation of a positive centre at C6 via the electron withdrawing property of the ester group attached to C5. This effect should not be ignored since it has direct influence on C4 centre by which the attached proton appears at low field strength (δ 4.0-5.0) in the ^{1}H-NMR spectra of their compounds, which is not usual for this type of structure.



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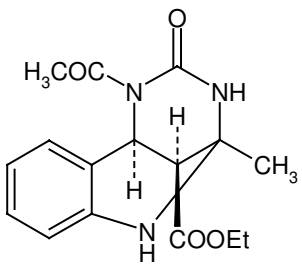

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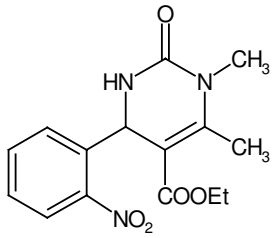
It is worth mentioning that in some related work reported recently[26] as well as in some work done in our laboratory,[27] an acyl substituent on the nitrogen atom at position-3 has direct influence on the proton at C4, resulting in more shift to a lower field strength (δg.7-6.5). This led us to recall the cyclisation reaction affected by acetic anhydride reported by Baldwin;[22] it is possibly due to the creation of a positive centre at C6 (via induction), which is produced by the acetyl group attached to N3, which was formed upon using acetic anhydride.

Our interest in the above point prompted us to prepare 4-(2-aminophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-caboxylic acid ethyl ester (**19**), which could be obtained in approximately quantitative yield by reduction of the corresponding nitro compound by using palladised charcoal and ammonium formate (without using a source of heat or radiation as reported by Baldwin). Treating **19** with acetic anhydride did not give the expected **20** but a mixture of products, which are still under investigation.



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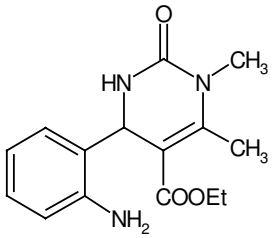

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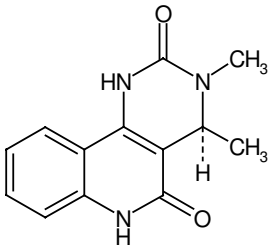

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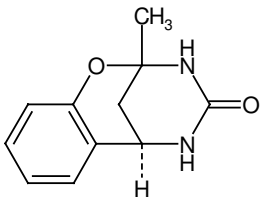

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An interesting cyclisation occurred when 1,6-dimethyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**21**) was reduced by the method mentioned above, where 3,4-dimethyl-4,6-dihydro-1H,3H-pyrimido[5,4-c]quinoline-2,5-dione (**23**) was obtained directly via elimination of ethanol and cyclisation. This cyclisation is not surprising since the N1-methyl substituent facilitates the hydrolysis of the ester group.[28] The uncyclised compound **22** was formed by using 1/10 w/w Pd/C/compound, while using double the amount of Pd/C produced the cyclised **23**.

The key for determining the structures of the oxacyclic compounds is the position of the methyl group attached to C3 of the pyrimidine ring in their ^{1}H-NMR spectra, which appeared at a higher magnetic field when compared with the uncyclised compounds; there is a shift by about 0.7 ppm towards higher field strength. This shift was observed clearly with the compound obtained by alkaline hydrolysis of compound **13**, which suffered decarboxylation to furnish 9-methyl-8-oxa-10,12-diaza-tricyclo-[7.3.1.0^{2,7}]trideca-2-(7),3,5-trien-11-one (**24**),[29] in which the methyl group appears at δ 0.5 ppm.

Experimental

Melting points were recorded on a capillary melting point apparatus and are uncorrected. The IR spectra were recorded with a Philips Infracord Spectrophotometer Model PU9712 in KBr discs. NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a JEOL-270 spectrometer with Me_4Si as an internal standard. Mass spectra were obtained with a Shimadzu GCS-QP 1000 EX spectrometer at 70eV. Elemental analysis was performed at the Microanalytical Laboratory of the National Research Centre. The results of elemental analysis, melting points, and yields for compounds **8-14** are given in the Table.

Table. Physical and analytical data of compounds 8-14.

Compd. No.	mp °C	Yield %	Molecular formula (Mol. Wt.)	Analysis Calcd./Found		
				C%	H%	N%
8	134-137	67	$C_{14}H_{15}N_3O_6$ (321.29)	52.34 52.20	4.71 4.80	13.08 12.90
9	177-179	88	$C_{14}H_{15}N_3O_5S$ (337.36)	49.85 49.70	4.48 4.60	12.46 12.25
10	185-188	85	$C_{15}H_{18}N_2O_5$ (306.32)	58.82 58.80	5.92 6.00	9.15 9.05
11	156-159	92	$C_{15}H_{18}N_2O_4S$ (322.39) 9.95	55.89 55.75	5.63 5.70	8.69 8.60
12	210-212	70	$C_{15}H_{16}N_2O_6$ (320.30)	56.25 56.25	5.04 5.00	8.75 8.70
13	200-203	83	*Ref. 24*			
14	204-207	87	*Ref. 24*			

General procedure for preparation of 4-(substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (8-12) and substituted 9-methyl-11-oxo(thioxo)-8-oxa-10,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylic acid ethyl ester, compounds 13-17 and 18.

A mixture consisting of urea (1.32 g, 22 mmol), or thiourea (1.67 g, 22 mmol), salicylaldehyde derivative (10 mmol), ethyl acetoacetate (1.6 mL, 12 mmol), ethanol (75 mL), and acetic acid (2 mL) was heated under reflux for several hours until completion of the reaction (6-12 h, monitored by TLC). The solvent was removed under reduced pressure; the solid obtained was treated with 50 mL of water and filtered, washed with water, dried, and crystallised from ethanol.

Compound **15**, mp 182-185 ^{o}C, ^{1}H-NMR (d_6-DMSO, δ ppm): 9.15 (d, 1H, J = 3 Hz, N1-H), 7.90 (dd,J = 3 Hz & 7.0 Hz, 1H, ArC3-H), 7.85 (dd, J = 3 Hz & 7.0 Hz, 1H, ArC5-H), 7.20 (d, 1H, J = 3 Hz, N3-H), 7.05 (d, 1H,J = 7.0 Hz, 1H, ArC6-H), 5.30 (d, 1H, C1-H), 3.95 (q, 2H, CH_2), 3.36 (d, 1H, C13-H), 2.29 (s, 3H, CH_3) and 1.05 (t, 3H, CH_3). MS: 321.2 (100%), Analysis: For $C_{14}H_{15}N_3O_6$ (321.29), Calcd: C, 52.34; H, 4.71; N, 13.08; Found: C, 52.20; H, 4.80; N, 12.85.

Compound **16**, mp 179-181 ^{o}C, ^{1}H-NMR (d_6-DMSO, δ ppm): 9.2 (s, 1H, OH), 7.75 (s, 1H, NH), 6.95 (d, J=3 Hz, 1H, NH), 6.80-6.60 (m, 3H, Ar-Hs), 5.30 (d,J = 3 Hz, 1H, C1-H), 3.95 (q, 2H, CH_2), 3.30 (d, 1H, C13-H), 2.29 (s, 3H, CH_3) and 1.15 (t, 3H, CH_3). MS: 292.10 (45%), 278.10 (100%); Analysis: For $C_{14}H_{16}N_2O_5$ (292.23) Calcd: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.50; H, 5.55; N, 9.45.

Compound **17**, mp 170-172 ^{o}C,^{1}H-NMR (d_6-DMSO, δ ppm): 8.75 (s, 1H, NH), 7.85 (d, J = 3 Hz, 1H, NH), 7.45 (s, 1H, OH), 6.80-6.60 (m, 3H, Ar-Hs), 5.20 (d,J = 3 Hz, 1H, C1-H), 3.95 (q, 2H, CH_2), 3.30 (d, 1H, C13-H), 2.22 (s, 3H, CH_3) and 1.05 (t, 3H, CH_3). MS: m/z 308.10 (100%); Analysis: For $C_{14}H_{16}N_2O_4S$ (308.35) Calcd:. C, 54.53; H, 5.23; N, 9.08; Found: C, 54.53; H, 5.23; N, 9.08.

14,16-Diaza-7,13-dimethyl-8,12-dioxa-5,15-dioxo-tetracyclo-[11.3.1.0^{4,9}][O$^{2,-11}$]-heptadeca-2,4(9),6,10-tetraene-17-carboxylic acid ethyl ester (18) was isolated as a mixture of 2 configurational isomers of approximately equal ratio as indicated by its NMR spectrum; their presence as 2 overlapped spots on its TLC analysis made their separation difficult. mp 236-240 ^{o}C, ^{1}H-NMR ($CDCl_3$, δ ppm) showed 2

signals, at δ 6.61 and 6.60 (2s, 2H, C6-Hs), 6.57 & 6.50 (2s, 2H, 2NHs), 6.08 & 6.04, (2s, 2H, NHs), 5.99 (2s, 2H, C10-Hs), 5.05 & 5.00 (2s, 2H, C1-Hs), 4.27 (q, 2H, CH_2-ester), 4.20 (q, 2H, CH_2-ester), 3.97 & 3.95 (2s, 6H, $2OCH_3$), 3.22 & 3.02 (2s, 2H, C17-Hs), 2.28 (s, 6H, CH_3-pyranone ring), 1.9 & 1.83 (2s, 6H, $2CH_3$), and 1.31 and 1.16 (2t, 3H each, $2CH_3$-ester). MS: m/z 388 12%, and base peak ion at 328 [M^+-(OC_2H_5 + CH_3)]. Analysis: For $C_{19}H_{20}N_2O_7$ (388.38), Calcd: C, 58.76; H, 5.19; N, 7.21%; Found: C, 58.70; H, 5.25; N, 7.10%.

4-(2-Aminophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (19)

6-Methyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester was prepared from 2-nitrobenzaldehyde by the method described above, mp 215-218 °C (reported 220 °C).[23] One gram of the product was suspended in methanol (50 mL) and cooled in an ice bath, to which was added 0.1 g of Pd/C (10%) followed by 4 mL of water containing 1 g of ammonium formate. The mixture was stirred at room temperature until completion of the reaction (monitored by TLC, 24 h). The reaction mixture was filtered, washed with methanol, the filtrate was concentrated under vacuum, water was added to the residue, and the product was filtered and dried. It was crystallised from methanol to give colourless crystals, mp 189-191 °C (187-188 °C).[23] MS (m/z, %): 276 (M^+, 26); 202 (M^+-CO_2Et, 100%); ^{1}H-NMR (d_6-DMSO, δ ppm): 9.05 (s, 1H, NH), 7.27 (d, 1H, NH), 6.95 (t, 1H, ArC_4-H), 6.91 (d, 1H, ArC_6-H), 6.65 (d, 1H, ArC_3-H), 6.52 (t, 1H, ArC_5-H), 5.30 (d, 1H, C_4-H), 4.91 (s, 2H, NH_2), 3.95 (q, 2H, CH_2), 2.29 (s, 3H, CH_3) and 1.05 (t, 3H, CH_3).

1,6-Dimethyl-4-(2-aminophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**22**)

1,6-Dimethyl-4-(2-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester (**21**) was prepared from 2-nitrobenzaldehyde, methyl urea, and ethyl acetoacetate by the method described herein, mp 165-168 °C (methanol), ^{1}H-NMR ($CDCl_3$, δ ppm): 7.86 (d,J=6.5 Hz, 1H, ArC_3-H), 7.54 (t, 1H, ArC_4-H), 7.38 (d & t, 2H, ArC_5-H&6), 6.0 (s, 1H, N_3-H), 5.74 (d, J=2.7 Hz, 1H, C_4-H), 3.90 (q, 2H, CH_2-), 3.25 (s, 3H, N-CH_3), 2.63 (s, 3H, CH_3), and 0.91 (t, 3H, CH_3-ester). Analysis: for $C_{15}H_{17}N_3O_5$, (319.32), calcd. %: C, 56.42; H, 5.37; N, 13.16, found: C, 56.35; H, 5.30; N, 13.15.

The foregoing product (**21**) was reduced with Pd/C by the procedure described herein to give compound **22**, mp 95-98 °C. MS: 289 (M^+, 8%), 216 (M^+-COOEt, base peak). ^{1}H-NMR (d_6 DMSO)s 7.50 (d, J =10 Hz, 1H, NH), 6.92 (t, 1H, ArH-C5‘), 6.85 (d, 1H, ArC_6-H), 6.65 (d, 1H, ArC_3-H), 6.50 (t, 1H, ArC_4-H), 5.25 (d, J =10 Hz, 1H, C4), 4.95 (s, 2H, NH_2), 4.00 (q, 2H, CH_2), 3.10 (s, 3H, CH_3) and 1.05 (t, 3H, CH_3-ester). Analysis: for $C_{15}H_{19}N_3O_3$(289.34), calcd.: C, 62.27; H, 6.62; N, 14.52; found: C, 62.10; H, 6.70; N, 14.50%.

3,4-Dimethyl-4,6-dihydro-1H,3H-pyrimido[5,4-c]quinoline-2,5-dione (23)

The same method of reduction described above for the formation of compound **22** was applied except that 2-fold excess of Pd/C was used. Yield: 76%, mp 285-298 °C; ^{1}H-NMR (d_6 DMSO, δ ppm) of **23**, δ 11.1 (b, 1H, NH-quinoline), 9.75 (s, 1H, NH), 8.35 (d,1H, Ar-H), 7.65 (t, 2H, Ar-Hs), 7.25 (t, 1H, Ar-H), 4.6 (q, 1H, C_6-H), 2.95 (s, 3H, N-CH_3), and at 1.30 (d, 3H, CH_3). MS: 244 (M^++1), and other ions due to successive loss of the OH, and CH_2 groupings. IR (KBr, υ cm^{-1}) showed absorption peaks at 3237, 3187 (NHs), 1679, 1630 (CO amides). Analysis: for $C_{13}H_{13}N_3O_2$ (243.27), Calcd.: C, 64.19; H, 5.39; N, 17.27% Found: C, 64.10; H, 5.35; N, 17.20%.

9-Methyl-8-oxa-10,12-diaza-tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-11-one (24)

The starting pyrimidine **13** (2.76 g, 10 mmol) was dissolved in absolute ethanol (10 mL) to which was added sodium hydroxide solution (20 mL, 20%). The mixture was allowed to stand for 4 h and then was heated under reflux for a further 2 h, (monitored by TLC). After completion of the reaction, the mixture was acidified with dil. HCl and kept at room temperature overnight; the solid obtained was filtered off, washed with water, and dried. Crystallisation from dilute ethanol (80%) gave 1.4 g (68% yields) of **24**, mp 283-285 °C. MS: 203 (M^+-1, 33%), 189 (M^+-Me + H, 100%). ^{1}H-NMR (d_6 DMSO, δ ppm), 7.33 (s, 1H, NH), 7.16 (m, 2H, Ar-Hs), 7.0 (d, 1H, NH), 6.85 (t, 1H, Ar-C_4-H), 6.75 (d, 1H, Ar-C_3-H), 4.24 (q, 1H, C_1-H), 2.15 (d, 2H, C_{13}-H) and 1.6 (s, 3H, CH_3). IR spectrum showed neither peaks due to phenolic OH nor the carbonyl ester (C=O). Analysis: for $C_{11}H_{12}N_2O_2$ (204.23), calcd.: C, 64.69; H, 5.92; N, 13.72%, found: C, 64.50; H, 6.10; N, 13.90%.

Conclusion

In the 1-pot 3-component Biginelli reaction, the steric proximity of the OH substituent in the *ortho* position of the aromatic ring, and the C6 carbon of the pyrimidine ring enables the formation of a 6-membered ring via intramolecular Michael addition. This addition reaction is prevented by the presence of oxygen bearing moiety neighbouring to the hydroxyl group.

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