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Synthesis and Stereochemistry of β-Arylethenyl α-Hydroxyalkyl Ketones

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Some new β-arylethenyl α-hydroxyalkyl ketones were prepared. Their U.V., I.R. and N.M.R. data are given and their stereochemistry is discussed.

Synthese und Stereochemie von α-Hydroxy-dialkyl-aryliden-ketonen

Mehrere neue α-Hydroxy-dialkyl-aryliden-ketone wurden synthetisiert. Ihre U.V., I.R. und N.M.R.-Charakteristika sind angegeben und ihre Stereochemie wird diskutiert.

In a former paper we reported that the oximes corresponding to the hydroxyketones $RR'C(OH)\text{-}CO\text{-}CH_3$ possess a neurotropic activity[1]. So we tried to synthesize the hydroxyketones $RR'C(OH)\text{-}CO\text{-}CH{=}CH\text{-}C_6H_4\text{-}R''$. Our interest in these compounds is both pharmacological, because of their resemblance to the former molecules, and chemical, because of the numerous possible isomers.

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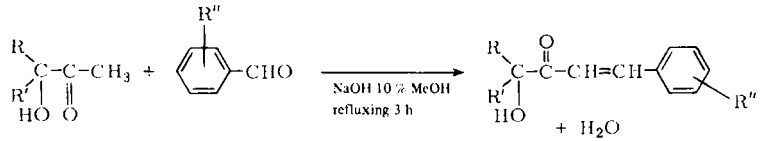
Hitherto of few papers have been published about α-hydroxy dialkyl arylidene ketones. In the literature only references to 20 molecules of this type are found, all of them bearing $R=R'=CH_3$, except two with RR'C=cyclohexyl[2-5]. All of them had been prepared by an alsolisation-ketolisation reaction.



The condensation of the aldehyde with the appropriate ketone is performed in the presence of basic catalysts. *Scheibler* and *Fischer*[2] use 10 % dilute aqueous sodium hydroxide in absolute ethanol for 48 h, *Vartanyan* and *Nazarov*[3,4] sodium methanolate for 24 h only. We proceeded by immediately heating in 10 % soda in methanol; the reaction took only 3 hours. In this way we prepared 12 new compounds. All the experiments using hydrochloric acid as a catalyst were unsuccessful.

Stereochemistry

The α-hydroxy arylidene ketones show three different types of steric isomerism.

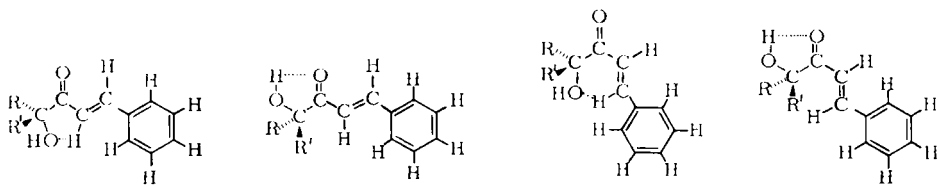
When R is different from R' enantiomerism is possible due to the chiral carbon atom.

The position of the substituents of the ethylenic double bond leads to a Z,E isomerism.

The rotation around the 2,3 bond gives two conformers: cisoid S, cis, and transoid S, trans.

After study of molecular models it seems that the Z isomer is to be totally excluded; the only remaining possibilities thus are E, s-cis and E, s-trans. Another question may be raised: is it possible for the tertiary hydroxyl group, which rotates freely round the RR'C-CO bond to be fixed in the plane of the cinnamoyl system by an intramolecular hydrogen bonding. In order to clearify this, the OH band was studied by IR spectroscopy..Chloroformic solutions of all the compounds were studied. The existence of an intramolecular bond could be demonstrated.

Stereochemistry of the α-Hydroxydialkyl Arylidene Ketones



E, S-cis (anti) E, S-cis (syn) E, S-trans (anti) E, S-trans (syn)

Spectral data

Ultra-violet

The R and R' groups have little influence on the λ max values. The substitution of the benzene nucleus leads to a bathochrom displacement. The 2'-chloro substituted derivative is the only one that produces a light hypsochrom shift at λ max 1. (Fig. 1 and 2).

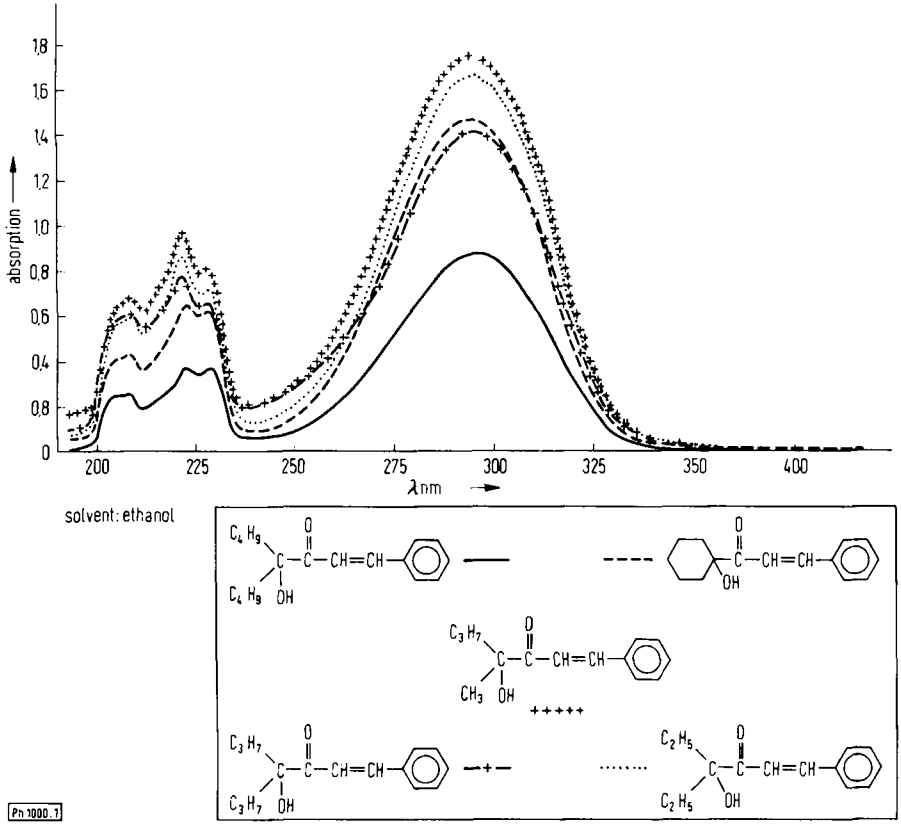


Fig. 1:

Infra-Red

A simple empirical relation was established between the position and the intensity of the vibrations and the stereochemistry of the ketones[6].

Several rules have been proposed for the determination of the conformations.

Study of the frequency shifts $\Delta \nu : \nu_{C=O} - \nu_{C=C}$. The shift is greater for S,cis (cisoid) isomer than for S, trans (transoid). *Erskine*[7], *Braude* and *Timmons*[8] proposed limit values. *Cottee*[9] gives more accurate values and indicates $\Delta \nu > 70$ cm^{-1} for S,cis conformation and $\Delta \nu < 60$ cm^{-1} for S, trans conformation.

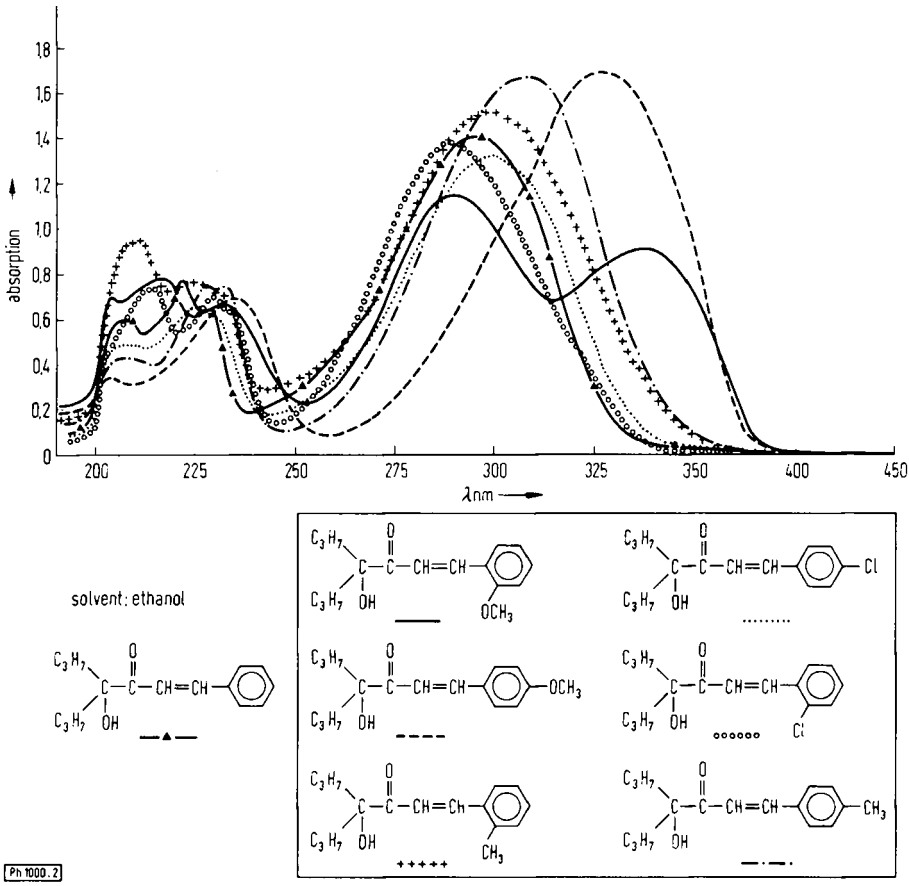


Fig. 2:

Study of the $\nu_{C=O}$ and $\nu_{C=C}$ intensity bonds ($I_{C=O}$ and $I_{C=C}$). They are about identical for S,cis α,β unsaturated ketones while for S, trans isomers, $\nu_{C=O}$ absorption is much higher.

S, cis: $I_{C=O} \simeq I_{C=C}$
S, trans: $I_{C=O} > I_{C=C}$

The ratio of integrated intensity $I_{C=O} / I_{C=C}$ lies between 0,7 and 3,5 for S,cis conformations. It is higher than 6 for s,trans conformations. All the α-hydroxy dialkyl arylidene ketones studied have an absorption band in the 980–990 cm^{-1} zone; it can be attributed to the deformation vibration of ethylenic ν_{CH}. They all belong to (E) configuration. This agrees with the fact that only the (E) configuration is compatible with the plane imposed by the cinnamoyl system of molecules.

The C=C vibration bonding shows an intensive absorption in the 1590–1620 cm^{-1} region. Its intensity is very close to the $\nu_{C=O}$ vibration and generally is higher. So we can claim that the α-hydroxy dialkyl arylidene ketones studied have a cisoid conformation. This is conformed by the fact that the $\Delta\nu = \nu_{C=O} - \nu_{C=C}$ varies from 70 to 75 cm^{-1}.

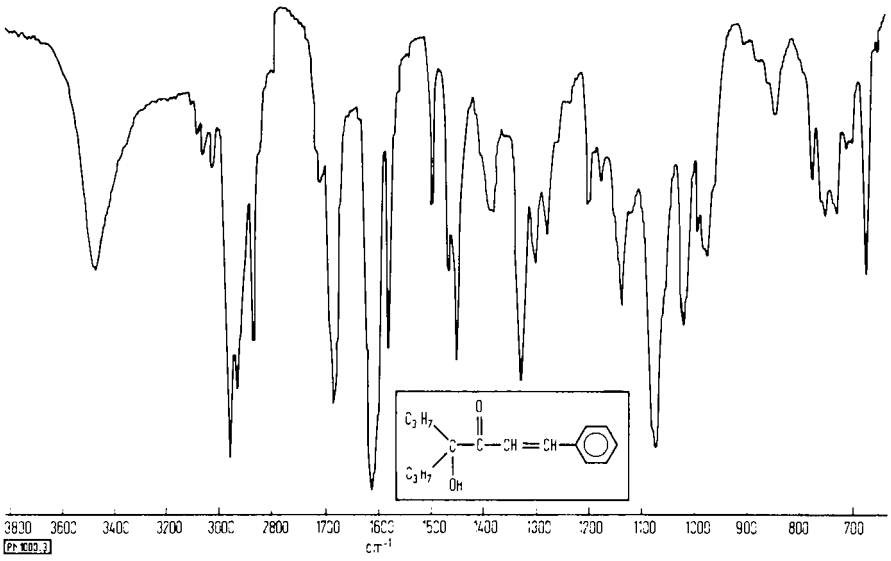


Fig. 3: Infra-Red Spectrum of Hydroxy-4-propyl-4-phenyl-1-hepten-1-one-3

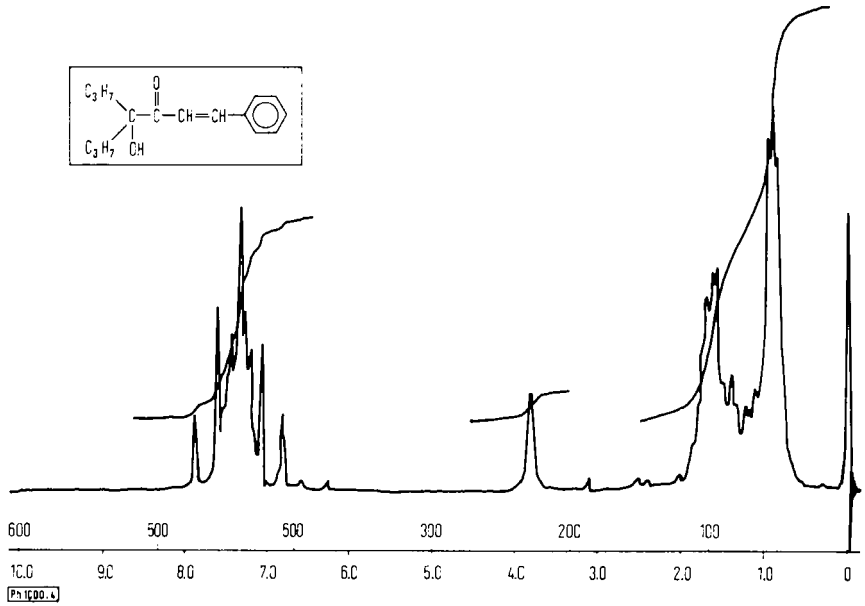


Fig. 4: NMR Spectrum of Hydroxy-4-propyl-4-phenyl-1-hepten-1-one-3 in CCl_4

Nuclear Magnetic Resonance

The values of the coupling constant ($J_{H'H}$) of the two ethylenic protons constitutes the best criterion for configuration. High values of this constant (11 to 18 Hz) are characteristic for an E configuration, as well as J_{AB} being equal to 15–16 Hz.

The cisoid or transoid conformations of the α, β ethylenic ketones established by A.S.I.S. effect (aromatic induced shift[10,11]). The A.S.I.S. effect was determined for each H_A and H_B proton by the difference of their chemical shifts in hexadeuterated benzene towards carbon tetrachloride. The very low negative values for H_A proton confirm that the α-hydroxy dialkyl arylidene ketones have cisoid conformation.

Table 1: *NMR Data of* **1–12** [δ (ppm)]

Nr.	OH	OH	OCH_3		CH_3		H_A			Δ [a]	H_B		
	CCl_4	C_6D_6	CCl_4	C_6D_6	CCl_4	C_6D_6	CCl_4	C_6D_6	H_A	H_B	CCl_4	C_6D_6	J_{AB}(Hz)
1	4,25	4,35	–	–	1,40	1,40	7,73	7,87	−0,14	0,03	7,13	7,10	15
2	3,90	4,15	–	–	–	–	7,72	7,86	−0,14	0,01	7,04	7,03	15
3	3,82	4,24	–	–	–	–	7,71	7,95	−0,24	0,09	6,97	7,06	16
4	3,65	4,00	–	–	–	–	7,60	7,70	−0,10	0,08	6,88	6,80	15
5	3,70	4,05	–	–	–	–	8,09	–	–	–	6,95	–	16
6	3,76	4,30	3,76	3,25	–	–	7,62	7,94	−0,32	0,43	6,72	7,15	16
7	3,85	4,25	3,85	3,20	–	–	8,05	8,48	−0,43	0,15	7,00	6,85	16
8	3,82	4,26	–	–	2,30	2,10	7,70	7,90	−0,20	0,10	6,90	7,00	15
9	4,05	4,25	–	–	2,35	3,15	8,08	8,18	−0,10	0,01	7,02	7,01	16
10	3,75	4,12	–	–	–	–	7,67	7,85	−0,18	−0,10	6,88	6,98	16
11	3,60	4,10	–	–	–	–	7,68	8,00	−0,32	−0,27	7,05	7,32	16
12	3,85	4,25	–	–	–	–	8,60	–	–	–	7,05	–	16

a $\Delta = {}^{\delta} CCl_4 - {}^{\delta} C_6D_6$.

Pharmacological data

None of the dialkyl arylidene ketones showed the expected pharmacological effect; however, a neurotropic activity was stated for pyridinic analogs[12].

None of the molecules had any notable activity as psychotropics, analgesics or anti-inflammatoric agents. No anti-convulsant activity was found by oral procedure at 200 mg/kg. The same procedure showed practically no toxicity for 400 mg/kg.

We are especially grateful to *Madeleine Broll* and *Pierre Eymard* (Head of the C.R.E.P. centre d'études et de recherches pharmacologiques, groupe Labaz) for the pharmacological results.

Experimental Section

Chemistry

Melting points: in capillary tubes on a F.P. 1 Mettler apparatus. *I.R. spectra*: IR 4230 Beckman, using films or KBr pills. *NMR spectra*: Hitachi Perkin Elmer R24 (60 MHz) in $CDCl_3$ and C_6D_6. *UV*: SP 800 Unicam in ethanolic solution.

Ethyl-4-hydroxy-4-phenyl-1-hexen-1-one-3

All the compounds were obtained by the same method. The preparation of the cetols has already been described in a former publication[1]. The preparation of the above compound is given as an example.

6 g NaOH are dissolved in 60 ml of methanol. 20 ml of the 10 % solution are added to 13.02 g (0.1 mol) of ethyl-3 hydroxy-3 pentanone-2. Benzaldehyde 10.6 g (0.1 mol) is added drop by drop to the warm solution, then the remaining 40 ml of the 10 % NaOH solution is added. Methanol is evaporated under vacuum. The aqueous solution treated by 60 ml of 10 % hydrochloric acid is vigorously shaken and extracted with diethyl ether. The residue is distilled under reduced pressure. bp_2 = 130–135°. $C_{14}H_{18}O_2$ (218,3) Calc: C 77.1, H 8.31; Found: C 77.1, H 8.28.

Pharmacology

Tests were carried out on male OF_1 mice. The drugs were administered in a suspension of olive oil. The tests that were generally used were described in a previous paper[13].

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Table 2: *Analytical Data of* **1–12**

Nr.	R	R′	R″	m.p. b.p.	crist. solv.	Formula M.	C calc.	C found	H calc.	H found	Cl calc.	Cl found
1	CH_3	C_3H_7	H	135–138/2	–	$C_{14}H_{18}O_2$ 218,3	77,1	77,2	8,31	8,05		
2	C_2H_5	C_3H_7	H	130–135/2	–	$C_{14}H_{18}O_2$ 218,3	77,1	77,1	8,31	8,28		
3	C_3H_7	C_3H_7	H	150–155/2	–	$C_{16}H_{22}O_2$ 246,35	78,0	78,0	9,00	8,73		
4	C_3H_7	C_3H_7	Cl (4′)	88,4°	Hexane	$C_{16}H_{21}ClO_2$ 280,8	68,5	68,6	7,53	7,48	12,6	12,5
5	C_3H_7	C_3H_7	Cl (2′)	63,1°	Hexane	$C_{16}H_{21}ClO_2$ 280,8	68,5	68,5	7,53	7,35	12,6	12,9
6	C_3H_7	C_3H_7	OCH_3 (4′)	93–94°	Hexane	$C_{17}H_{24}O_3$ 276,38	73,9	74,0	8,75	8,73		
7	C_3H_7	C_3H_7	OCH_3 (2′)	180–185/1	–	$C_{17}H_{24}O_3$ 276,38	73,9	73,8	8,75	8,50		
8	C_3H_7	C_3H_7	CH_3 (4′)	92°	Ethanol	$C_{17}H_{24}O_2$ 260,38	78,4	78,7	9,29	9,19		
9	C_3H_7	C_3H_7	CH_3 (2′)	150–155/0,5	–	$C_{17}H_{24}O_2$ 260,38	78,4	78,2	9,29	9,42		
10	C_4H_9	C_4H_9	H	61°	Ethanol	$C_{18}H_{26}O_2$ 274,41	78,8	78,6	9,55	9,60		
11	C_6H_{10}		H	61,1°	Pentane/ Ether	$C_{15}H_{18}O_2$ 230,31	78,2	78,1	7,87	7,94		
12	C_3H_7	C_3H_7	naphthyl	98°	Hexane	$C_{20}H_{24}O_2$ 296,41	81,0	81,0	8,16	8,12		