THE CLAISEN-SCHMIDT REACTION WITH HETEROCYCLIC ANALOGS OF o-HYDROXYACETPHENONE

III. Condensation of 4-Hydroxy-3-Acetyl-6-Methylpyrid-2-One, and its N-Methyl and N-Phenyl Derivatives with Aromatic Aldehydes*

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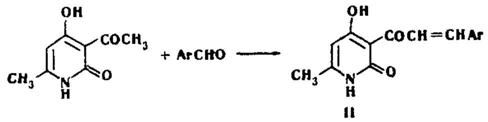
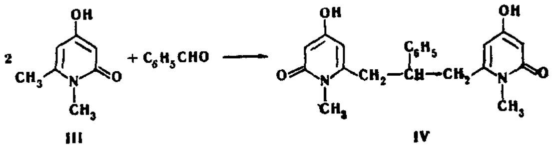
Claisen-Schmidt condensation of 4-hydroxy-3-acetyl-6-methylpyrid-2-one, and its N-methyl and N-phenyl derivatives with aromatic aldehydes is investigated, and it is shown that the products of this reaction are 3-cinnamoyl and not 6-styryl derivatives.

It was previously shown [1–3] that dehydracetic acid (4-hydroxy-3-acetyl-6-methylpyrone), which can be regarded as a heterocyclic analog of o-hydroxyacetophenone, readily undergoes the Claisen reaction. Further investigation of this reaction showed [4] that a mixture of cis and trans isomers of 4-hydroxy-3-cinnamoyl-6-methyl-pyrone-2 was formed in the condensation process.

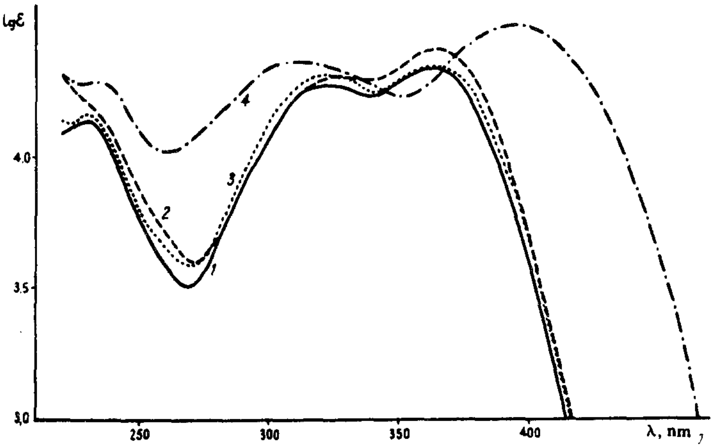
The investigation of this reaction was extended to the nitrogen analog of dehydracetic acid, 4-hydroxy-3-acetyl-6-methylpyrid-2-one (I), and its N-methyl and N-phenyl derivatives previously described [5–7]. In all cases reaction gave yellow or orange crystalline substances (see figure and table), which had sharp melting points after one recrystallization, and which were shown by paper chromatography to each consist of a single individual. Other isomers could not be isolated from the mother liquors. Evidently, unlike what obtains with dehydracetic acid, here only derivatives of trans-4-hydroxy-3-cinnamoyl-6-methylpyrid-2-one (II) are formed.



However, for conclusive proof of the structures of the compounds prepared, it was necessary to check whether the 6-methyl group of I underwent condensation with an aldehyde. In this connection benzaldehyde was condensed with 4-hydroxy-1, 6-dimethylpyrid-2-one (III), and the product was found to be 1, 3-bis(4'-hydroxy-1'-methyl-2'-pyrid-6'-onyl)-2-phenylpropane (IV).



The structure of IV was confirmed by determination of its Rast molecular weight and by use of mass spectroscopy (spectrum showed a molecular ion peak at m/e 366), as well as by elementary analysis and synthesis from 1,3-bis(4'-hydroxypyron-2'-yl-6')-2-phenylpropane and methylamine.



UV spectra (in ethanol): 1) 4-Hydroxy-3-cinnamoyl-6-methylpyrid-2-one; 2) 4-hydroxy-3-cinnamoyl-1-phenyl-6-methylpyrid-2-one; 3) 4-hydroxy-3-cinnamoyl-1,6-dimethylpyrid-2-one; 4) 4-hydroxy-3-cinnamoyl-6-styryl-1-methyl-pyrid-2-one.

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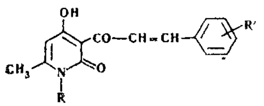
*For Part II see [6]



Derivatives of 4-Hydroxy-3-cinnamoyl-6-methylpyrid-2-one

R	R′	Reaction time, hr	Mp, °C	Formula	Found, %			Calculated, %			UV spectrum		Yield, %
					C	H	N	C	H	N	λ_{max}, nm	lg ε	
H	H	1 3	262.5—263.5	$C_{15}H_{13}NO_3$	70.49	5.36	5.20	70.58	5.49	5.13	232 323 364	4.15 4.26 4.34	85.2[a] 39.2[b]
H	*m*-NO_2	4	277—278[c]	$C_{15}H_{12}N_2O_5$	60.13 59.97	3.80 3.87	9.34	60.00	4.03	9.33	305 364	4.27 4.20	55.5
H	*p*-Cl	4.5	313—314	$C_{15}H_{12}ClNO_3$	—	—	4.99	—	—	4.83	233 327 365	4.16 4.33 4.38	55.5
H	*p*-OH	4.5	288—289	$C_{15}H_{13}NO_4$	66.45 66.29	4.72 4.73	5.20 5.35	66.41	4.83	5.16	247 387	4.11 4.46	55.7
H	*p*-$N(CH_3)_2$	4	284.5—285[c]	$C_{17}H_{18}N_2O_3$	68.50 68.34	5.98 6.08	9.32	68.44	6.08	9.39	257 348 446	4.05 3.90 4.56	56.3
CH_3	H	1	158—159	$C_{16}H_{15}NO_3$	71.11	5.39	5.53	71.36	5.61	5.20	232 323 364	4.15 4.30 4.34	89[a]
CH_3	*p*-NO_2	2	248.5—249.5	$C_{16}H_{14}N_2O_5$	61.16	4.64	8.74 8.80	61.14	4.49	8.91	324 370	4.38 4.26	40
CH_3	*m*-NO_2	3	235—235.5	$C_{16}H_{14}N_2O_5$	61.32	4.25	8.84 8.66	61.14	4.49	8.91	307 365	4.32 4.22	43
CH_3	*p*-Cl	4	193—194	$C_{16}H_{14}ClNO_3$	63.53	4.89	4.53 4.23	63.27	4.65	4.61	234 328 367	4.16 4.36 4.39	60
CH_3	*p*-OH	4	262—263	$C_{16}H_{15}NO_4$	67.29	5.21	4.95 5.06	67.36	5.30	4.91	246 384	4.15 4.54	53.5
CH_3	*p*-$N(CH_3)_2$	2	236—236.5	$C_{18}H_{20}N_2O_3$	69.20	6.45	9.29	69.21	6.45	8.97	259 353 449	3.94 3.80 4.41	52
C_6H_5	H	8	211.5—212.5	$C_{21}H_{17}NO_3$	75.83	5.14	4.19	76.00	5.18	4.22	328 365	4.30 4.40	70[d]
C_6H_5	*p*-OH	8	271—272	$C_{21}H_{17}NO_4$	72.56	4.64	3.83 3.81	72.61	4.93	4.03	249 386	4.14 4.53	65.3
C_6H_5	*p*-$N(CH_3)_2$	1	272—273	$C_{23}H_{22}N_2O_3$	—	—	7.47 7.71	—	—	7.42	260 350 460	3.99 3.89 4.49	58.5
C_6H_5	*p*-Cl	8	219—220	$C_{21}H_{16}ClNO_3$	68.74 68.61	4.62 4.52	3.99 3.89	68.95	4.41	3.83	331 365	4.35 4.41	51.3

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[a] Prepared by method b. [b] Prepared by method a. [c] Mp in sealed capillary. [d] Prepared by method b, using 40% KOH.

Only when benzaldehyde was condensed with 4-hydroxy-3-cinnamoyl-1, 6-dimethylpyrid-2-one by prolonged boiling (25 hr), was the corresponding styryl derivative, 4-hydroxy-3-cinnamoyl-6-styryl-1-methylpyrid-2-one obtained, and the yield was insignificant. Its UV spectrum differed markedly from that of the starting compound (see figure).

Hence it can be regarded as established that the 3-acetyl group of I participates in condensation with aromatic aldehydes.

EXPERIMENTAL

4-Hydroxy-3-acetyl-6-methylpyrid-2-one was prepared as described in [2], mp 259.5°-260.5° C.

4-Hydroxy-3-acetyl-1, 6-dimethylpyrid-2-one was prepared as described in [5], yield 26.5%, mp 133.5°-134.5° C.

4-Hydroxy-3-acetyl-1-phenyl-6-methylpyrid-2-one was prepared as described in [8], yield 60%, mp 223°-224° C, the literature gives 217°-218° C [8].

4-Hydroxy-1, 6-dimethylpyrid-2-one was prepared as described in [9], yield 60%, mp 224°-225° C, the literature [9] gives mp 225°-226° C.

1, 3-Bis(4'-hydroxypyr-2'-onyl-6')-2-phenylpropane was prepared as described in [10], yield 47%, mp 216°-217° C, the literature gives [10]mp 215° C.

Condensation of I with aromatic aldehydes. a) 0.018 mole I, 0.018 mole aldehyde, 20 ml pyridine, and a few drops of pyridine, were refluxed together for a few hours. After cooling, the precipitate was filtered off, (if necessary, part of the pyridine was distilled off), washed with pyridine, dried, and recrystallized from EtOH or pyridine.

b) 0.018 mole I, 0.018 mole aldehyde, 20 ml 10% NaOH, and 20 ml MeOH were refluxed together for 1 hr, cooled, neutralized with dilute HCl, and the precipitate of II filtered off. The II compounds prepared are shown in the table.

1, 3-Bis(4-hydroxy-1'-methylpyrid-2'-on-6-yl)-2-phenylpropane. a) 0.0072 mole 4-Hydroxy-1, 6-dimethylpyrid-2-one, 0.0072 mole benzaldehyde, 10 ml pyridine, and 2-3 drops of piperidine were refluxed together for 2 hr, the mixture cooled, the solid filtered off, was with pyridine, dried, and recrystallized from EtOH, yield 1.2 g (45.5%), mp 296°-297° C (sealed capillary). Found: C 69.80: H 6.33; N 7.82%, calculated for $C_{21}H_{22}N_2O_4$: C 68.84; H 6.05; N 7.65%, λ_{max} 293 nm, lg ε (4.155).

b) 0.00294 mole 1, 3-Bis(4'-hydroxypyr-2'-onyl-6')-2-phenylpropane, 0.00588 mole methylamine (25% aqueous solution), and 2 ml water were heated together for 1 hr at 100° C in a sealed tube. After cooling the products were treated with acetone, the precipitate filtered off, washed with acetone, and dried, yield 0.35 g (32.8%), mp 296°-297° C, undepressed mixed mp with the compound prepared by method *a*. The UV spectrum plots were identical.

4-Hydroxy-3-cinnamoyl-6-styryl-1-methylpyrid-2-one. 0.0028 mole 4-Hydroxy-3-cinnamoyl-1, 6-dimethylpyrid-2-one, 0.0028 mole benzaldehyde, 10 ml pyridine, and a few drops of piperidine were refluxed together for 25 hr. The reaction products were cooled, the pyridine removed under vacuum at room temperature, and the residue treated with acetone. The precipitate was filtered off, washed with acetone, and dried, yield 0.12 g (8.7%), mp 199.5°-200.5° C. Found: C 77.24; 77.17; H 5.51; 5.30; N 3.86; 3.71%, calculated for $C_{23}H_{19}NO_3$: C 77.29; H 5.36; N 3.92%. λ_{max} 232, 310, 396 nm, lg ε 4.29; 4.35; 4.49.

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