BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 43 3937—3938 (1970)

The Reactions of Dihydropyridones (II)

Noboru SUGIYAMA, Makoto YAMAMOTO and Choji KASHIMA

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Tokyo

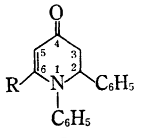
(Received June 17, 1970)

As dihydropyridones are typical β-amino-enones which are sterically fixed to a *cis*-s-*trans* structure,[1] it is interesting to examine the difference in its reactivity from β-amino-enones of other types. Recently, we reported on the protonation, oxidation, reduction,[2] photoisomerization,[3] and the relation between the structure and the spectral properties of dihydropyridone.

The present paper will describe the aldol condensation of dihydropyridone and related reactions.

6-Methyl-1,2-diphenyl-2,3-dihydro-4-pyridone (**1**) was treated with benzaldehyde in an alkaline ethanol solution. The expected condensation product at C-3 methylene was not detected, but an unexpected product, 1,2-diphenyl-6-styryl-2,3-dihydro-4-pyridone (**2**) was obtained in a 33% yield. From the spectral data and elemental analyses, the structure of **2** was determined.

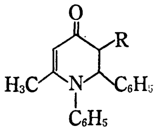
The mechanism of the formation of **2** can be explained as follows: C-6 methyl is more active than C-3 methylene, and benzaldehyde condenses at C-6 methyl to give 6-(β-hydroxyphenethyl)-1,2-diphenyl-2,3-dihydro-4-pyridone (**3**), which then produces **2** by the elimination of water.



1: R = $-CH_3$
2: R = $-CH{=}CH{-}C_6H_5$
3: R = $-CH_2CHC_6H_5$ (with OH below CH)

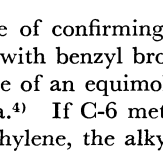
$-CH_2\underset{\displaystyle OH}{\underset{|}{C}}HC_6H_5$

4: R = $-CH_2CH_2C_6H_5$



5: R = $-CH_2C_6H_5$
7: R = $-CH \cdot C_6H_5$

$-\underset{\displaystyle OH}{\underset{|}{C}}H \cdot C_6H_5$



6

Fig. 1.

For the purpose of confirming this, the alkylation reaction of **1** with benzyl bromide was carried out in the presence of an equimolar sodium amide in liquid ammonia.[4] If C-6 methyl is more reactive than C-3 methylene, the alkylation product at C-6 methyl, 6-phenethyl-1,2-diphenyl-2,3-dihydro-4-pyridone (**4**), may be expected to be produced. In fact, dihydropyridone **4** was obtained, and a trace of the alkylation product at C-3 methylene,

---

[1] C. Kashima, M. Yamamoto and N. Sugiyama, *J. Chem. Soc.*, *C*, **1970**, 111.

[2] C. Kashima, M. Yamamoto and N. Sugiyama, This Bulletin, **42**, 2690 (1969).

[3] C. Kashima, M. Yamamoto, Y. Sato and N. Sugiyama, *ibid.*, **42**, 3596 (1969).

[4] N. Sugiyama, M. Yamamoto and C. Kashima, *ibid.*, **42**, 1357 (1969).

3-benzyl-6-methyl-1,2-diphenyl-2,3-dihydro-4-pyridone (**5**), was detected.

The formation of **5** shows that C-3 methylene has a reactivity. In order to confirm this, **1** was treated with benzaldehyde in the presence of two molar equivalents of sodium amide in liquid ammonia. When two molar equivalents of a base are used in liquid ammonia, the dianione (**6**) of **1** will be produced, and it is expected that the C-3 methylene position will be more reactive than that of C-6 methyl, much as is the case with the dipotassium salt of acetylacetone in liquid ammonia.[5]

From the reaction mixture, 3-(α-hydroxybenzyl)-6-methyl-1,2-diphenyl-2,3-dihydro-4-pyridone (7) was obtained in a 25.5% yield. No condensation product at C-6 methyl was detected. The structure of **7** was proved by the spectral data and by the results of elemental analyses.

The C-6 methyl of dihydropyridone **1** is the most reactive in the molecule, and aldol condensation occurred at this position. This is a novel type of aldol condensation. C-3 methylene has some reactivity in liquid ammonia, but this position is less reactive than C-6 methyl.

Experimental

6-Methyl-1,2-diphenyl-2,3-dihydro-4-pyridone (1). Compound **1** was prepared from acetylacetone and benzylidenaniline in the presence of three moles of potassium amide in liquid ammonia.[4] NMR (in $CDCl_3$): τ 8.13 (singlet, 3H, C-6 methyl protons), 7.09 (double quartet, 2H, C-3 methylene protons), 5.08 (quartet, 1H, C-2 methine proton), 4.81 (singlet, 1H, C-5 olefin proton), and 2.6—3.2 (multiplet, 10H, aromatic protons).

1,2-Diphenyl-6-styryl-2,3-dihydro-4-pyridone (2). To a solution containing 0.5 g of **1** and 0.3 g of benzaldehyde in 20 m*l* of ethanol, a 5% sodium hydroxide solution (10 m*l*) was added. The reaction vessel was closed with a rubber stopper to prevent oxidation, and, after shaking for 10 min, the mixture was left to stand at room temperature for 12 hr. The mixture was then poured into 50 g of crushed ice and 200 m*l* of water, and acidified with dilute hydrachloric acid. The aqueous solution was extracted with chloroform. The organic layer was washed with water two times, and then dried over calcium chloride. After the removal of the solvent, the residue was chromatographed on a silica-gel (Merck 7729) column with a benzene-ethyl acetate (4 : 1 *v/v*) mixture. A fraction which showed R_f 0.35 upon silica-gel (Wako gel B-5) thin-layer chromatography with a benzene-ethyl acetate (4 : 1 v/v) mixture was collected to give 220 mg (33%) of **2**, as yellow plates; mp 164—165°C.

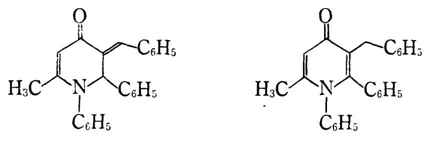
Found: C, 85.06; H, 6.11; N, 3.97%. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99%.
IR (KBr): 1630, 1535, 755 and 690 cm^{-1}.
UV: λ_{max}^{EtOH} 236 (ε 14200), 314 mμ (ε 20600).
$\lambda_{max}^{HCl/EtOH}$ 235 (ε 11900), 353 mμ (ε 28900).
NMR (in $CDCl_3$) (τ): 7.25, 6.69 (double quartet, 2H, C-3 methylene protons), 4.86 (quartet, 1H, C-2 methine proton), 4.80 (singlet, 1H, C-5 olefin proton), 3.58 (doublet, 1H, α-olefin proton of the C-6 styryl group, $J_{\alpha\beta}=16.5$ Hz) and 2.56—2.90 (multiplet, 16H, β-olefin proton of the C-6 styryl group and aromatic protons).

The Condensation of 1 with Benzyl Bromide. In a 200-m*l*, three-necked flask, about 150 m*l* liquid was placed; 0.20 g of metalic sodium was then added to produce sodium amide. To this solution 2.0 g of **1** was added, and it was stirred for an hour; then equimolar benzyl bromide (1.23 g) in 10 m*l* of anhydrous ether was added. After stirring for one hour, the mixture was neutralized with excess solid ammonium chloride. The liquid ammonia was rapidly evaporated on a water bath, and to the residue there was added about 100 m*l* of water. The aqueous layer was extracted with ether, and the ethereal layer was washed with water and dried over anhydrous sodium sulfate. The formation of **4** and **5** was confirmed by thin-layer chromatography by a comparison of their R_f values with those of authentic specimens.[4]

3-(α-hydroxybenzyl)-6-methyl-1,2-diphenyl-2,3-dihydro-4-pyridone (7). In the presence of two molar equivalents of sodium amide, 1.32 g of **1** were allowed to react with equimolar benzaldehyde. The crude reaction product was purified by silciag-el (Merck 7729) column chromatography. The eluting solvent: benzene-ethyl acetate (2 : 1 v/v). Yield, 0.47 g of **7** (25.5%); colorless prisms; mp 122—123°C.

Found: C, 81.12; H, 6.30; N, 3.63%. Calcd for $C_{25}H_{23}NO_2$: C, 81.26; H, 6.28; N, 3.79%.
IR(KBr): 3380, 1625, 1550, 710 and 695 cm^{-1}.
UV: λ_{max}^{EtOH} 338 mμ (ε 16900).
NMR (in $CDCl_3$)(τ): 8.00 (singlet, 3H, methyl protons), 7.20 doublet, 1H, methine proton), 5.63 (singlet, 1H, methine proton), 5.01 (doublet, 1H, methine proton), 4.69 (singlet, olefin proton), 2.72—3.24 (multiplet, 15H, aromatic protons) and 6.25—7.20 (broad, 1H, hydroxy proton, disappeared by D_2O).

The Treatment of 7 with Concentrated Sulfuric Acid. To 200 mg of **7**, 10 m*l* of concentrated sulfuric acid were added; the mixture was then allowed to stand at room temperature for two hours. To the reaction mixture were added about 50 g of crushed ice, and the resulting suspension was extracted with chloroform. The chloroform layer was washed with water and then dried over calcium chloride. However, the expected product, **8** or **9**, was not detected by thin-layer chromatagraphy.[6]



8 **9**

Fig. 2.

---

[5] C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).

[6] G. R. Clemo and H. J. Johnson, *J. Chem. Soc.*, **1930**, 2136.