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Reaction of 2,3-Dihydro-4-pyridone

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In a previous paper we described the synthesis of 2,3-dihydro-4-pyridones from a Schiff base and β-diketones in the presence of excess potassium amide in liquid ammonia.[1] 2,3-Dihydro-6-methyl-1,2-diphenyl-4-pyridone (I), which was synthesized

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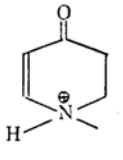
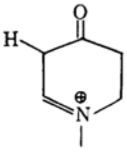
[1] N. Sugiyama, M. Yamamoto and C. Kashima This Bulletin **42**, 1357 (1969).

from acetylacetone and benzylidenaniline, is a typical enamino ketone. The reactions of 2,3-dihydro-4-pyridone have so far not been found in literature. This paper deals with the reactions of I, especially protonation, oxidation and reduction.

Protonation. Generally, β-enamino ketones can be protonated on nitrogen atom, α-carbon atom or oxygen atom.[2] Thus, the protonation of I is expected to give one of the products of three types A, B or C.


A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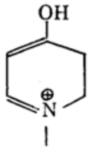

C

The ultraviolet absorption spectrum of the hydrochloride (II) showed the absorption maximum at 325 mμ. Compared with the absorption maximum of I at 327 mμ, the chromophore of II is the same as that of I. The methine proton signal at C-2 carbon is broad triplet in the NMR spectrum of II.

If the protonated product is type A, the methine proton of C-2 carbon is coupled to NH proton and broadened. In the infrared absorption spectrum of II, the strong absorption band appeared at 2250 cm^{-1}, which was assigned to more strongly hydrogen bonded hydroxyl group or the tertiary ammonium group. But the infrared absorption spectrum of the hydrobromide (III) showed a strong absorption band at 2420 cm^{-1}, 170 cm^{-1} apart from that of II. The results also suggest that I is protonated as shown in A.[3]

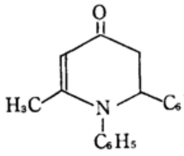
Oxidation. The dihydro heteroaromatic system containing nitrogen is known to play an important role as hydrogen donor in a biological oxidation-reduction system. By the hydrogen transfer reaction with chloranil, a typical hydrogen acceptor,[4] I gave a pyridone derivative, 6-methyl-1,2-diphenyl-4-pyridone (IV), which was synthesized by the condensation of 1-phenyl-1,3,5-hexanetrione with aniline.[5]

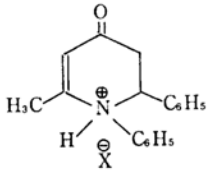
The treatment of I with mercuric acetate was also examined, because benzoquinolidine derivative, which has dihydropyridone neuclei, is oxidized to its hydroxypyridine derivative by mercuric acetate.[6] In this reaction IV was also produced.

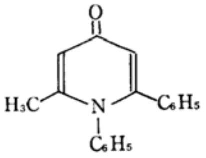
On the other hand, Kehrmann reported[7] that flavanes were oxidized with iodine to flavones. When the same oxidation method was applied to I, the expected oxidation product was not produced, an unexpected product being obtained.

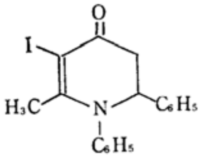
The ultraviolet spectrum of product V showed the absorption maximum at 360 mμ. In the NMR spectrum, similar to I, the aromatic protons, methylene protons and the methine proton appeared at τ 2.70, τ 6.78 and τ 4.99 respectively. The methyl protons appeared as a singlet at τ 7.65, and olefinic proton disappeared.

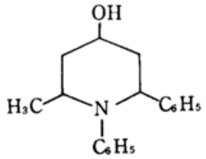
From these spectral data and the results of the elemental analyses, V was determined to be 2,3-dihydro-5-iodo-6-methyl-1,2-diphenyl-4-pyridone. In this reaction, it is supposed that iodine was added to the double bond of I and then was eliminated as hydroiodide.

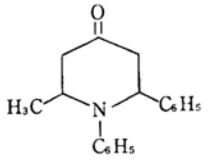

(I)


(II): X=Cl, (III): X=Br


(IV)


(V)


(VI)


(VII)

Reduction. By treatment of I with excess sodium borohydride, 6-methyl-1,2-diphenyl-4-piperidinol (VI) was obtained. The infrared spectrum showed the hydroxyl band at 3320 cm^{-1}, but no band of carbonyl and double bond. Both 240 mμ and 327 mμ disappeared in the ultraviolet spectra of VI. From these spectral data and the results of the elemental analyses, the structure of VI was determined.

On the other hand, the hydrogenation of I in acetic acid catalyzed by platinum oxide gave two

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[2] H. E. A. Kramer, *Ann.*, **696**, 15 (1966).

[3] E. A. V. Ebsworth and N. Sheppard, *Spectrochim. Acta*, **13**, 261 (1959).

[4] E. A. Braude, J. Hannah and Sir R. Linstead, *J. Chem. Soc.*, **1960**, 3249.

[5] S. Boatman, S. E. Smith, G. F. Morris, W. G. Kofron and C. R. Hauser, *J. Org. Chem.*, **32**, 3817 (1967).

[6] M. von Strandtmann, M. P. Cohen and J. Shavel, Jr., *ibid.*, **31**, 797 (1966).

[7] F. Kehrmann, *Ber.*, **39**, 922 (1906).

products, VI and 6-methyl-1,2-diphenyl-4-piperidone (VII). In the infrared spectrum of VII the carbonyl absorption band appeared at 1715 cm^{-1}, but the double bond band in the region of 1660—1600 cm^{-1} disappeared. In the NMR spectrum of VII, methyl protons are split to the doublet at τ 9.20. Two methylene protons appeared at τ 7.20 and 7.40, and C-2 methine proton appeared as a triplet at τ 4.10.

Under the same conditions, however, the hydrogenation of IV failed, and IV was quantitatively recovered. It is clear that the reduction of dihydropyridone is much easier than that of the corresponding pyridone.

All these reactions confirm that the dihydropyridone (I) favors the enamino ketone structure, but there exists some tautomeric iminoenol structure which is responsible for hydrogen transfer reaction.

Experimental

2,3-Dihydro-6-methyl-1,2-diphenyl-4-pyridone (I). In liquid ammonia, I was prepared by the procedure described in a previous paper,[1] mp 84—85°C.

IR(KBr): 1640, 1560 and 700 cm^{-1}. UV: λ_{max}^{EtOH} 240 mμ (ε 2180), and 327 mμ (ε 10400).

2,3-Dihydro-6-methyl-1,2-diphenyl-4-pyridone Hydrochloride (II). A mitxure of 200 mg of I and 0.1 m*l* of concentrated hydrochloric acid in 5 m*l* of ethanol was maintained for 5 min at room temperature. By the evaporation of solvent under reduced pressure, 150 mg of II was obtained, which was recrystallized from acetone to give analytical pure substance, mp 173°C (decomp).

IR (KBr): 3050, 2250, 1620, 1500, 1215, 760 and 680 cm^{-1}. UV: λ_{max}^{EtOH} 327 mμ (ε 16900).

2,3-Dihydro-6-methyl-1,2-diphenyl-4-pyridone Hydrobromide (III). III was obtained from I and hydrobromic acid by the same procedure for II, mp 153°C (decomp).

IR (KBr): 3050, 2420, 1615, 1500, 1210, 760 and 680 cm^{-1}. UV: λ_{max}^{EtOH} 327 mμ (ε 14200).

Oxidation of I by Chloranil. A solution of 120 mg of I and 120 mg of chloranil in 10 m*l* of tetrahydrofuran was refluxed for 4 hr. The reaction mixture was cooled and 50 mg of crystal was collected, mp 235°C (lit. 242°C[5]). This crystal was identified with the authentic sample, which was obtained by condensation of 1-phenyl-1,3,5-hexanetrione with aniline,[5] by means of thin layer chromatography, infrared and ultraviolet absorption spectra.

Oxidation of I by Mercuric Acetate. To a solution of 500 mg of I in 5 m*l* of acetic acid was added 640 mg of mercuric acetate. The mixture was refluxed for 2.5 hr and then mixed with 20 m*l* of water. The aqueous solution was neutralized with dilute ammonia and extracted with benzene. After removal of the solvent, the residue was identified with the sauthentic sample by means of thin layer chromatography.

2,3-Dihydro-5-iodo-6-methyl-1,2-diphenyl-4-pyridone (V). A mixture of 100 mg of I, 300 mg of iodine, 150 mg of anhydrous potassium acetate and 10 m*l* of ethanol was refluxed for 4 hr. The reaction mixture was mixed with 100 m*l* of water, made alkaline with aqueous ammonia, and extracted with ether. The ethereal solution was washed with aqueous sodium thiosulfate and water. After removal of ether, the residue was recrystallized from ethanol-water mixture to afford 100 mg of V, mp 151°C.

Found: C, 54.71, 54.77; H, 4.16, 4.15; N, 3.70, 3.51; I, 33.91%. Calcd for $C_{18}H_{16}INO$: C, 55.54; H, 4.14; N, 3.60; I, 32.61%.

IR (KBr): 3050, 1640, 1510, 1200, 730 and 710 cm^{-1}. UV: λ_{max}^{EtOH} 302 mμ (ε 3200), 352 mμ (ε 11700).

The Sodium Borohydride Reduction of I. A mixture of 130 mg of I, 36.5 mg of sodium borohydride in 10 m*l* of ethanol was stirred at room temperature. After 8 hr, the reaction mixture was acidified with hydrochloric acid and then neutraized with aqueous ammonia. This aqueous solution was extracted with ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed by silica gel (Merck 7729) column with benzene-ethyl acetate (1 : 1 v/v) mixture. A fraction, which showed the R_f 0.49 on silica gel (Wako gel B-5) thin layer chromatography with benzene-ethyl acetate (1 : 1 v/v) mixture, was collected. After removal of the solvent, the residue was recrystallized from benzene, mp 84—85°C.

Found: C, 80.63; H, 8.04; N, 5.21%. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%.

IR (KBr): 3320, 1600, 1370, 1020 and 695 cm^{-1}. UV: λ_{max}^{EtOH} 253 mμ (ε 1250), 259 mμ (ε 1020) and 265 mμ (ε 780).

The Catalytic Hydrogenation of I. In the presence of 14.1 mg of platinum oxide, 200 mg of I in 10 m*l* acetic acid was hydrogenated at 30°C and atmospheric pressure. After absorption of 20 m*l* of hydrogen the reaction was stopped. After the catalyst was filtered off, the filtrate was poured into water and made alkaline with aqueous ammonia, and was extracted with ether. The ethereal solution was washed with water and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was separated on silical gel (Wako gel B-5) thin layer chromatograpny. The spots with the R_f 0.29 and 0.49 were identified with I and VI respectively. The product, which showed the R_f 0.71, was separated by means of silica gel (Merck 7729) column chromatography with benzene-ethyl adetate (1:1 v/v) mixture to give V.

IR (liquid film): 1715, 1600, 1375, 1220, 740 and 700 cm^{-1}.

NMR Spectra. NMR spectra were measured by a Hitachi H-60 high resolution Neuclear Magnetic Resonance Spectrometer. The solvent was deuterochloroform and TMS was used as the internal standard.