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Syntheses of 2,3-Dihydro-4(1*H*)-pyridones

Noboru SUGIYAMA, Makoto YAMAMOTO and Choji KASHIMA

Department of Chemistry, Tokyo Kyoiku University, Otsuka, Bunkyo-ku, Tokyo

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The condensation of β-diketones with benzaldazine yields 1-benzylidenimino-2,3-dihydro-4-pyridones, which may be catalytically hydrogenolyzed to the corresponding 2,3-dihydro-4(1*H*)-pyridones. Some reactions of 2,3-dihydro-4(1*H*)-pyridones are discussed.

Previously we described that β-diketones may be condensed with benzylidenaniline in the presence of three molar equivalents of potassium amide in liquid ammonia to produce 1-phenyl-2,3-dihydro-4-pyridones.[1] We also reported that these 1-phenyl-2,3-dihydro-4-pyridones were prepared by the cyclization of the correspoding aminodiketones.

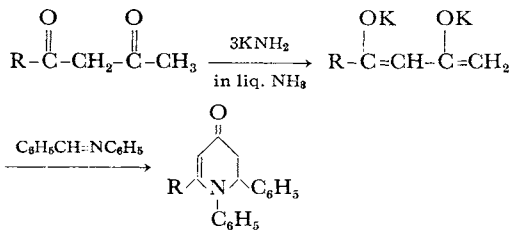


Fig. 1

However, the 1-unsubstituted dihydropyridones, namely 2,3-dihydro-4(1*H*)-pyridones are more important than 1-phenyl ones in view of the organic reactions and biochemical studies. Now we wish to report that β-diketones when condensed with benzaldazine give 1-benzylidenimino-2,3-dihydro-4-pyridones, which on hydrogenolysis lead to 2,3-dihydro-4(1*H*)-pyridones. The present paper also described some of the reactions of these compounds.

Results and Discussion

Acetylacetone (II) was condensed with benzaldazine (I) in the presence of three molar equivalents of sodium amide in liquid ammonia to give 1-benzylidenimino-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (V). The yield was 6.2%. When potassium amide was used instead of sodium amide, the yield of V increased to 11.0%.

The structure of V was determined from the spectral data and the elemental analyses (see Experimental). The nuclear magnetic resonance spectrum supported the structure of V, *i.e.*, the two singlets at τ 7.52 and 4.82 were assigned to the methyl and the olefinic protons. The ABX type signals in the region τ 6.49—7.70 were assigned to the C-3 methylene protons coupled with C-2 methine proton at τ 4.50 as a quartet. The signal at τ 2.40—3.05 displayed 10 aromatic protons and

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

TABLE 1. SPECTRAL DATA OF 2,3-DIHYDRO-4(1*H*)-PYRIDONES

Compound	IX	X	XI	XII
IR (cm^{-1}): ν_{NH}	3250 (m)[a]	3275 (m)	3250 (m)	3250 (s)[b]
$\nu_{C=O}$	1610 (s)	1615 (s)	1605 (s)	1610 (s)
$\nu_{C=C}$	1585 (s)	1555 (m)	1570 (m)	1575 (m)
UV: λ_{max}^{EtOH} mμ (ε)	315 (14500)	245 (14000) 339 (12200)	318 (14400)	318 (14100)
$\lambda_{max}^{EtOH\text{-}HCl}$ mμ (ε)	310 (10300)	277 (13300) 333 (10200)	312 (9950)	312 (10100)
NMR (in $CDCl_3$): (τ)				
NH	4.10 bs[c]	4.50 bs	4.41 bs	4.70 bs
Olefinic	5.07 s[d]	4.54 s	5.08 s	5.05 s
C-2 methine	5.34 q	5.12 q[e]	5.52 q	5.67 d[f]
J_{AX} (Hz)	12.0	12.0	12.0	
J_{BX} (Hz)	7.5	7.4	7.5	
C-3 methylene	7.2—7.9 m[g]	6.9—7.6 m	6.9—7.8 m	7.0—7.3 m

a) (m) medium b) (s) strong c) bs, broad singlet d) s, singlet e) q, quartet
f) d, doublet g) m, multiplet

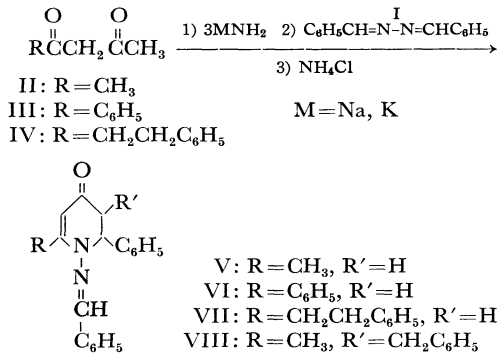


Fig. 2

a proton of –N=CH– group as a multiplet.

By the same procedure, 1-benzylidenimino-2,6-diphenyl-2,3-dihydro-4-pyridone (VI) was obtained in 9.2% yield from I and benzoylacetone (III). Using I and 6-phenyl-2,4-hexanedione (IV), 1-benzylidenimino-6-phenethyl-2-phenyl-2,3-dihydro-4-pyridone (VII) and its isomer 3-benzyl-1-benzylidenimino-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (VIII) were obtained in the yields of 52% and 21%, respectively. In the reaction of I and IV, the condensation took place not only at C-1 but also C-5 position of IV. The ratio of VII to VIII was about 5 : 2, similar to that of the reaction of IV with benzylidenaniline.

Schiff bases are reduced to secondary amines by hydrogen in the presence of nickel or platinum catalyst,[2] and hydrazocompounds are reduced to amines.[3] On the other hand, neither the carbonyl group nor the double bond of 2,3-dihydro-4-pyridone ring is hydrogenolyzed by platinum oxide catalyst in methanol or ethanol solution.[4] However, 2,3-dihydro-4-pyridone is reduced in the presence of platinum oxide to a corresponding 4-piperidinol or 4-piperidone in acetic acid solution.[5] When 1-benzylidenimino-2,3-dihydro-4-pyridone is catalytically hydrogenolyzed in the presence of platinum oxide in alcohol solution, 1-benzylamino- or 2,3-dihydro-4(1*H*)-pyridone may be expected. Hydrogenolysis of VII in ethanol catalyzed by platinum oxide gave only 2,3-dihydro-4(1*H*)-pyridone, 6-phenethyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (XI), but no 1-benzylaminodihydropyridone. The structure of XI was confirmed by the spectral data and the results of elemental analyses (see Table 1).

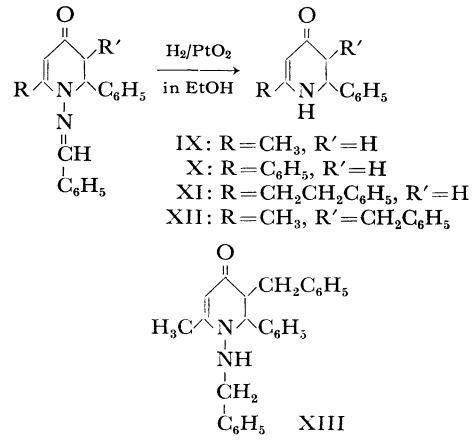


Fig. 3

By the same procedure, 6-methyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (IX), 2,6-diphenyl-2,3-dihydro-4(1*H*)-pyridone (X) and 3-benzyl-6-methyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (XII) were

2) a) C. F. Winans, *J. Amer. Chem. Soc.*, **61**, 3566 (1939). b) A. Skita and F. Keil, *Chem. Ber.*, **61**, 1682 (1928). c) A. Skita, F. Keil and H. Havemann, *ibid.*, **66**, 1400 (1933). d) A. Skita and F. Keil, *ibid.*, **61**, 1452 (1928).

3) G. Schultz, *Ber.*, **17**, 472 (1884).

4) Unpublished data by N. Sugiyama, M. Yamamoto and C. Kashima.

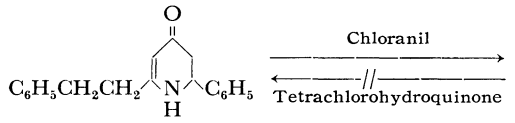
5) N. Sugiyama, M. Yamamoto and C. Kashima, This Bulletin, **42**, 2690 (1969).

obtained from V, VI and VIII, respectively. The spectral data are summarized in Table 1.

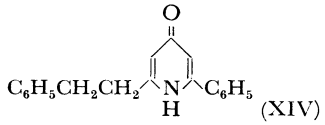
When equimolar hydrogen is absorbed, 1-benzylamino-2,3-dihydro-4-pyridone may be expected to be formed as an intermediate. However, after absorbing about 3/2 molar hydrogen, VIII gave 20% of 1-benzylamino-3-benzyl-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (XIII) together with 45% of XII.

The structure of XIII was proved by the spectral data. The infrared spectrum showed bands at 3300, 1630 and 1550 cm^{-1} for NH, conjugated carbonyl and C=C double bonds. The nuclear magnetic resonance spectrum showed at τ 6.33—6.66 (broad triplet, 1H) and τ 6.13 (doublet, 2H) for amino proton and methylene protons of 1-benzylamino group. By treatment with D_2O, the former disappeared and the latter changed to a singlet. The other signals are similar with those of VIII. From these results it is apparent that 1-benzylidenimino-2,3-dihydro-4-pyridone was first hydrogenolyzed to 1-benzylamino-2,3-dihydro-4-pyridone and this benzylamino compound underwent hydrogenolysis to yield the corresponding 2,3-dihydro-4(1*H*)-pyridone.

In a previous paper, we reported that 1-phenyl-2,6-disubstituted dihydropyridones were dehydrogenated in the presence of a hydrogen acceptor.[5] XI was also dehydrogenated by treating with chloranil in tetrahydrofuran to yield the corresponding pyridone, 6-phenethyl-2-phenyl-4(1*H*)-pyridone (XIV). XIV was identical with the authentic sample[6] on thin-layer chromatography. However, conversion from XIV into XI with tetrachlorohydroquinone was not successful. This proved that XI was easily oxidized with chloranil to XIV and the reaction was not of the equilibrium type.



(XI)



(XIV)

Fig. 4

It is well known that I is decomposed to hydrazine and benzaldehyde by treating with dilute acid. Taylor *et al.* reported[7] that the isopropylidenimino group of 3-isopropylidenimino-4(3*H*)-pteridinone undergoes a reductive elimination in dilute acid solution to give 3-amino-4(3*H*)-pteridinone. If VII is treated with dilute acid, the corresponding *N*-amino dihydropyridone is expected to produce.

Compound VII was treated with dilute hydrochloric acid, but *N*-aminodihydropyridone was not obtained, and instead of *N*-aminodihydropyridone, a red viscous substance, which could not be purified, was obtained.

The present method is generally applicable for the synthesis of 2,3-dihydro-4(1*H*)-pyridones.

Experimental

Syntheses of 1-Benzylidenimino-dihydropyridone. General Procedure: In a 500 m*l* three necked flask, about 300 m*l* of anhydrous liquid ammonia was introduced. A small amount of potassium was then added and completely dissolved. A catalytic amount of ferric chloride was then added to the stirred blue solution, followed by 4.7 g (0.12 g atom) of potassium in small portions. The solution turned dark gray within 90 min. To this solution was added 0.04 mol of β-diketone in 30 m*l* of anhydrous ether. After stirring for 45—60 min, 0.02 mol of I[8] in 50 m*l* of anhydrous ether was added. After stirring for another 3.5—4 hr at −33°C, 100 m*l* of ether was added from a dropping funnel, followed by the rapid evaporation of ammonia on a water both. To the ethereal solution, excess ammonium chloride (10 g) in 100 m*l* water was added. The ethereal layer was then separated and the aqueous layer was extracted with 100 m*l* of ether. The ethereal layer was washed with water and dried over anhydrous sodium sulfate. The remaining aqueous layer was acidified with dilute hydrochloric acid, and again extracted with 200 m*l* of chloroform. The chloroform extract was dried over calcium chloride. After concentration under reduced pressure, both residue gave condensation products.

The crude product was chromatographed on a silica gel (Merck 7734, 0.05—0.2 mm) column with a benzene-ethyl acetate mixture. The fraction showing a green color on a ferric chloride test was collected and concentrated *in vacuo* to give crude 1-benzylidenimino-2,3-dihydro-4-pyridone. The latter was then crystallized from ethyl acetate to yield pure dihydropyridone. By this procedure, V, VI, VII and VIII were obtained.

1-Benzylidenimino-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (V). From I and II, V was synthesized. Fractionating solvent: Benzene-ethyl acetate 2 : 1 (*v*/*v*) mixture. Pale yellow prisms, mp 176—177°C.

Found: C, 78.40; H, 6.42; N, 9.59%. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65%. IR (KBr): ν_{max} 1635 (νC=O), 1580 (νC=N) and 1560 cm^{-1} (νC=C). UV(mμ(ε)): λ_{max}^{EtOH} 229(9900), 234(9500), 282(3600) and 364(44000).

In this reaction, 72% of II and 49% of I were recovered. In spite of elongation of the reaction time (for 6.5 hr), the yield of V was 10.2% and 65% of II, 35% of I also recovered.

1-Benzylidenimino-2,6-diphenyl-2,3-dihydro-4-pyridone (VI). VI was prepared from I and III in

6) C. Kashima, M. Yamamoto, S. Kobayashi and N. Sugiyama, *ibid.*, **42**, 2389 (1969).

7) E. C. Taylor, O. Vogl and P. K. Loeffler, *J. Amer. Chem. Soc.*, **81**, 2479 (1959).

8) H. T. Bucherer and M. Schmidt, *J. Prakt. Chem.*, **79**, 369 (1909).

9.2% yield. Fractionating solvent: Benzene-ethyl acetate 4 : 1 (*v/v*). Yellow plates, mp 178—179°C.

Found: C, 81.88; H, 5.83; N, 8.06%. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95%. IR (KBr): ν_{max} 1645 (νC=O), 1570 (νC=N) and 1550 cm^{-1} (νC=C). UV(mμ(ε)): λ_{max}^{EtOH} 238(15400), 281(9430) and 368 (31700). NMR (in $DCCl_3$): τ6.36—6.76 (ABX type, quartet, 1H, C-3 methylene proton, J_{AB}=16.5 Hz, J_{AX}=7.5 Hz), 6.96—7.34 (ABX type, quartet, 1H, C-3 methylene proton, J_{BX}=1.5 Hz), 4.68 (singlet, 1H, C-5 olefinic proton), 4.40(quartet, 1H, C-2 methine proton) and 2.35—2.84 (multiplet, 16H, a proton of -N=CH- group and aromatic protons).

In this reaction, 57% of II was also recovered. But III was merely 18.5% recovered.

1-Benzylidenimino-6-phenethyl-2-phenyl-2,3-dihydro-4-pyridone (VII). VII was prepared from I and IV[9] in 52% yield. Fractionating solvent: Benzene-ethyl acetate 2 : 1 (*v/v*). Yellow plates, mp 118—121°C.

Found: C, 81.71; H, 6.34; N, 7.35%. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36%. IR (KBr): ν_{max} 1635 (νC=O), 1575 (νC=N) and 1550 cm^{-1} (νC=C). UV(mμ(ε)): λ_{max}^{EtOH} 231(12000), 236(11100), 283(3850) and 365(39000). NMR (in $CDCl_3$): τ 6.88 (singlet, 4H, phenethyl ethylene protons), 4.51—4.91(ABX type, quartet, 1H, C-3 methylene proton, J_{AB}=16.2 Hz, J_{AX}=7.4 Hz), 7.11—7.43(ABX type, quartet, 1H, C-3 methylene proton, J_{BX}=1.5 Hz), 4.81(singlet, 1H, C-5 olefinic proton), 4.50 (quartet, 1H) and 2.40—2.96 (multiplet, 16H).

3-Benzyl-1-benzylidenimino-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (VIII). VIII was obtained from the same reaction mixture as VII. On column chromatography with benzene-ethyl acetate 2 : 1 (*v/v*) VIII eluted ahead of VII. On silica gel (Wako gel B-500) thin layer chromatography with benzene-ethyl acetate 2 : 1 (*v/v*), VIII showed the R_f 0.37, while that of VII was 0.29. VIII was concentrated and recrystallized from benzene-*n*-hexane giving 21% yield. Yellow neeldes, mp 129—131°C.

Found: C, 81.32; H, 6.51; N, 7.27%. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36%. IR(KBr): ν_{max} 1640 (νC=O), 1580 (νC=N) and 1560 cm^{-1} (νC=C). UV(mμ(ε)): λ_{max}^{EtOH} 228(11800), 234(11100), 284(3280) and 363(28200). NMR (in $CDCl_3$): τ 6.68—7.32 (multiplet, 3H), 7.48 (singlet, 3H), 4.96 (singlet, 1H), 4.81 (singlet, 1H) and 2.40—3.30 (multiplet, 16H).

Reduction of 1-Benzylidenimino-2,3-dihydro-4-pyridones by Catalytic Hydrogenolysis: Using 100 mg of platinum oxide, 200—300 mg of 1-benzylidenimino-2,3-dihydro-4-pyridone in 30 m*l* ethanol was hydrogenolyzed at room temperature and atmospheric pressure. After absorbing about two molar equivalents of hydrogen the catalyst was filtered off. The ethanol solution was concentrated *in vacuo*, and the residue was chromatographed on a silica gel (Merck 7729, 0.08 mm) column with benzene-ethyl acetate 2 : 1 (*v/v*). Fractions showing a dark brown color with ferric chloride were collected, concentrated and recrystallized to give 2,3-dihydro-4-pyridone. IX, X and XI were prepared by this method. The spectral data are listed in Table 1.

6-Methyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (IX). IX was prepared by using 210 mg of V. Yield 62 mg (46%), colorless needles, mp 160—161°C.

Found: C, 76.92; H, 7.10; N, 7.73%. Calcd for $C_{12}H_{13}NO$: C, 76.97; H, 7.00; N, 7.48%.

2,6-Diphenyl-2,3-dihydro-4(1*H*)-pyridone (X). X was prepared from 200 mg of VI. Yield 92 mg (65.0%), yellow cubics, mp 149—151°C.

Found: C, 81.50; H, 6.13; N, 5.69%. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62%.

6-Phenethyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (XI). XI was obtained from 300 mg of VII in 92% (201 mg) yield, mp 124—126°C, colorless needles.

Found: C, 82.08; H, 6.95; N, 5.22%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05%.

3-Benzyl-6-methyl-2-phenyl-2,3-dihydro-4(1*H*)-pyridone (XII). VIII (250 mg) was hydrogenolyzed by the procedure described above. Twenty m*l* of hydrogen (calculated 31 m*l*) was absorbed and the product was chromatographed on a silica gel (Merck 7729) column with a benzene-ethyl acetate 2 : 1 (*v/v*) mixture. Fractions with R_f values 0.23 were collected and concentrated to give 65 mg (45%) of XII, colorless prisms, mp 159—160°C.

Found: C, 82.20; H, 6.89; N, 5.05%. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.91; N, 5.05%.

3-Benzyl-1-benzylamino-6-methyl-2-phenyl-2,3-dihydro-4-pyridone (XIII). From the same column, XIII was obtained. R_f value: 0.42. Yield, 51 mg (20%) as a yellow oil. UV(mμ): λ_{max}^{EtOH} 328. NMR(in $CDCl_3$): τ 7.80 (singlet, 3H, methyl protons), 7.20—6.70 (multiplet, 3H, C-3 methine proton and benzyl methylene protons), 6.66—6.33 (broad triplet, 1H, amino proton), 6.13 (doublet, 2H, methylene protons of benzylamino group), 5.41 (quartet, 1H, C-2 methine proton), 5.03 (singlet, 1H, C-5 olefinic proton) and 3.11—2.60 (multiplet, 15H, aromatic protons).

Dehydrogenation of XI. In 30 m*l* tetrahydrofuran were dissolved 80 mg of XI and 75 mg of chloranil. After refluxing for 5.5 hr, the mixture was cooled and the formation of XIV was confirmed on thin layer by the comparison with the authentic sample.[6]

Hydrolysis of VII. Compound VII (0.8 g) was dissolved in 40 m*l* of 50% aqueous ethanol and then 5 m*l* of concentrated hydrochloric acid was added. The mixture was refluxed for one hour on a water bath, and was made alkaline with sodium hydroxide. Extraction with chloroform and analysis of extract by means of silica gel (Wako gel B-500) thin layer chromatography (benzene-ethyl acetate, 2 : 1 *v/v*) showed two spots with R_f value 0.00 and 0.30. The latter was identified as VII. The former was a red viscous substance which could not be purified.

9) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960).