

The Ring-Opening Reaction of 1-Hydroxy-2-phenyl-1,2-dihydropyridine and Related Compounds

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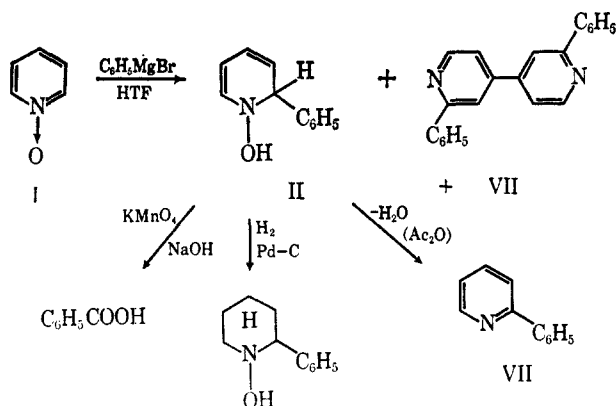
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Received May 31, 1967

Reaction of 1-hydroxy-2-phenyl-1,2-dihydropyridine (II) with an equimolar amount of benzoyl chloride in dry pyridine affords cinnamylidene acetonitrile (III) quantitatively. When the reaction is carried out under ice cooling, 1-benzoyloxy-2-phenyl-1,2-dihydropyridine (IV) is obtained which, on standing at room temperature, transforms into the isomer cinnamylidene acetaldehyde oxime benzoate (V).

In a previous paper¹ we reported that the reaction of pyridine 1-oxide (I) with phenylmagnesium bromide gave 1-hydroxy-2-phenyl-1,2-dihydropyridine (II) in good yield. The structural assignment was made on the basis of the chemical reactions shown in Chart I. Compound II is rather stable, and we have been focusing our attention on further investigations of its chemical behavior in view of its unique structure. The present paper reports the ring-opening reaction of II and related compounds.

CHART I



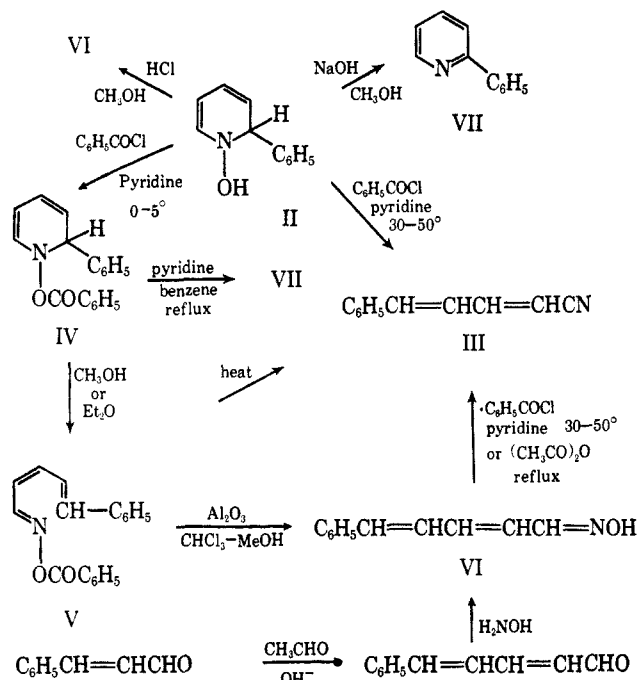
Treatment of II with an equimolar amount of benzoyl chloride in dry pyridine at room temperature converted it into a colorless oil, bp 106–107° (1 mm), in quantitative yield (Chart II). Elemental analysis established its empirical formula as $C_{11}H_9N$ (III), whereas the infrared spectrum exhibited a characteristic peak for a conjugated nitrile at 2212 cm^{-1} . This oil was characterized as cinnamylidene acetonitrile (III) by comparison of its infrared spectrum with that of an authentic sample prepared from cinnamylidene acetaldehyde according to the method reported by Vorlaender.²

These experiments showed that compound II, which can be regarded as an oxime, had undergone a Beckmann rearrangement resulting in the fission of the pyridine ring.

When this reaction was carried out under ice cooling, colorless needles of mp 78.5–79.5°, $C_{18}H_{15}O_2N$ (IV), were obtained. This product was unstable, and, on standing at room temperature in ether or ethanol, it was easily converted into the isomer, $C_{18}H_{15}O_2N$ (V), mp 157–158°.

2-Phenylpyridine (VII) was obtained when IV was refluxed in benzene containing a small amount of

CHART II



pyridine. On the other hand, heating of V gave no heterocyclic compound, but instead afforded cinnamylidene acetonitrile (III). Besides, when a solution of V in chloroform–methanol was passed through a column of alumina, it was hydrolyzed easily to give cinnamylidene acetaldoxime (VI). From these observations, it is clear that the structures of IV and V are 1-benzoyloxy-2-phenyl-1,2-dihydropyridine (IV) and cinnamylidene acetaldehyde oxime benzoate (V), respectively.

Moreover, treatment of II with hydrochloric acid in methanol afforded the ring-opened product (VI), but when II was refluxed in 3 *N* sodium hydroxide the starting material was recovered and VII was obtained in only a poor yield. This fact indicated that II is unstable toward acid so that the ring-opened product is obtained, whereas aromatization predominates in alkaline media to give VII.

For the sake of comparison, the same reaction was carried out with 1-hydroxy-2-phenyl-1,2-dihydroquinoline (VIII). As reported in a previous paper, the yield of the compound (VIII) was not satisfactory (25%), and therefore the Grignard reaction of quinoline 1-oxide with phenylmagnesium bromide was reinvestigated. Thus, treatment of quinoline 1-oxide with phenylmagnesium bromide in oxygen-free tetrahydrofuran under ice cooling increased the yield of VIII to 60%.

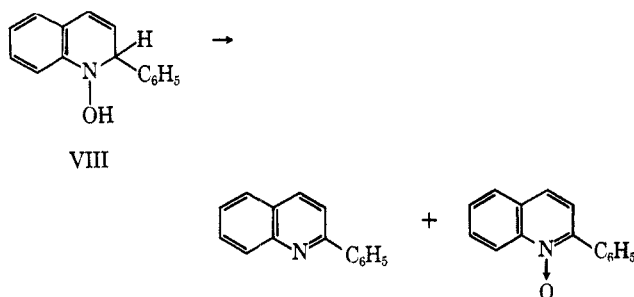
When VIII was treated similarly as in the case of

(1) T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965).

(2) D. Vorlaender and E. Daehn, *Ber.*, **62**, 542 (1929).

II, none of the ring-opened products was detected (Table I). For example, treatment of VIII with benzoyl chloride in pyridine or refluxing in methanolic hydrochloric acid afforded 2-phenylquinoline (IV) in good yield.

TABLE I



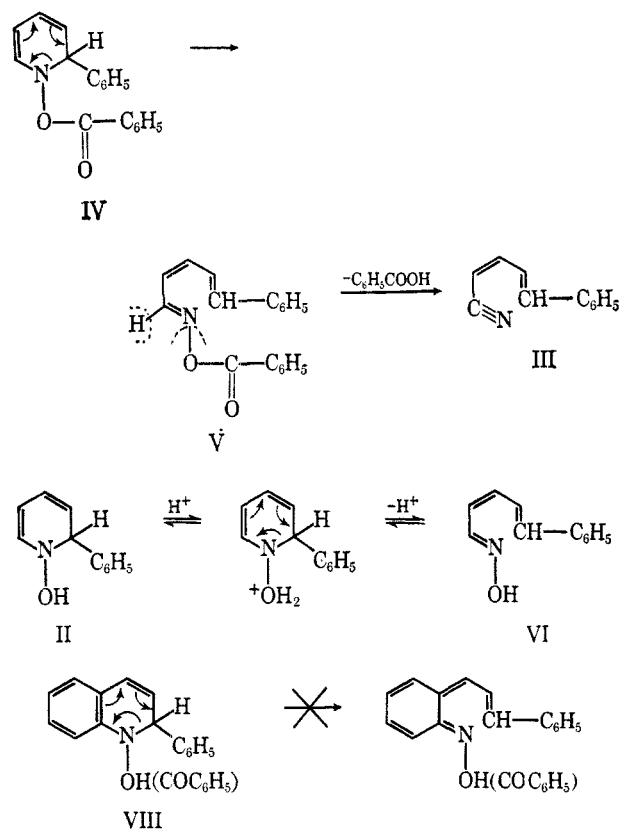
Reagent	Reaction conditions		Yield	
	Solvent	Temp	IX, %	X, %
C ₆ H ₅ COCl	Pyridine	0 ~ 5 ^a	90	
HCl	CH ₃ OH	Reflux ^b	80	
None	Pyridine	Reflux ^b	30	50
NaOH	H ₂ O-CH ₃ OH	Reflux ^b	50	

^a The reaction time was 10 hr. ^b The reaction time was 1 hr.

Although details of the mechanism of this reaction still remain obscure, a likely pathway is shown in Chart III. This mechanism also accounts for the resistance of VIII to C-N fission; namely, it will be difficult to contribute to the mesomerism as in the case of the pyridine derivatives (II).

In 1959, Hunt, *et al.*,³ reported that none of the

CHART III

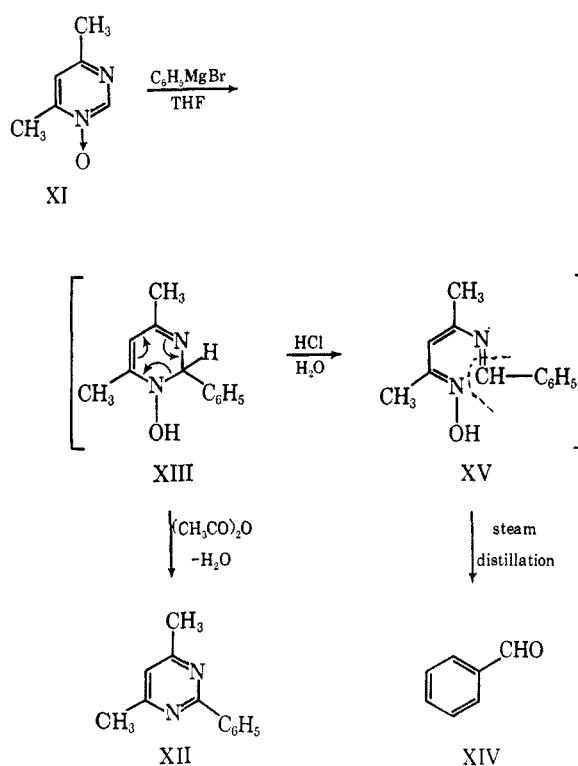


expected products was obtained by the reaction of 4,6-dimethylpyrimidine 1-oxide (XI) with phenylmagnesium bromide under the conditions reported by Colonna and Risaliti in the pyridine and quinoline series.⁴ However, if the Grignard reaction of XI in tetrahydrofuran proceeds similarly as in the case of pyridine 1-oxide (I), 2-phenyl-4,6-dimethylpyrimidine (XII) could be obtained by the subsequent treatment of the reaction product with acetic anhydride.

In view of the above-mentioned facts, the Grignard reaction of XI was reinvestigated. Thus, XI was treated with phenyl Grignard reagent in tetrahydrofuran under ice cooling, and the resulting residue, which was induced to crystallize with difficulty, was subsequently treated with acetic anhydride at room temperature, upon which XII was obtained in good yield; acidic hydrolysis of the crude reaction product, on the other hand, yielded benzaldehyde in good yield.

This fact shows that, owing to the similarity of the structure of the intermediate (XIII) to II, the ring fission reaction takes place resulting in formation of the C=N double bond of XV. Although XIII was not isolated as a crystalline substance, it is clear that the Grignard reaction of XI can be represented as shown in Chart IV.

CHART IV



Experimental Section

Reaction of 1-Hydroxy-2-phenyl-1,2-dihydropyridine (II) with Benzoyl Chloride. A.—To a solution of II (0.86 g) in dry pyridine (4 ml) was added dropwise benzoyl chloride (0.91 g) with stirring. After heating at 40–50° for 3 hr, the reaction mixture was poured into ice to give a brown oil, which was extracted with ether. The ether layer was washed with 10% hydrochloric acid, 10% sodium carbonate, and then with water. From the ether extract III was obtained as a colorless oil: bp 106–107° (1 mm); yield, 0.37 g (93%).

(3) R. Hunt, J. McOmie, and E. Sayer, *J. Chem. Soc.*, 525 (1959).

(4) M. Colonna and A. Risaliti, *Gazz. Chim. Ital.*, **83**, 58 (1953).

Anal. Calcd for $C_{11}H_9N$: C, 85.13; H, 5.85; N, 9.03. Found: C, 84.98; H, 5.99; N, 8.93.

Infrared analysis gave λ_{\max}^{liq} 2212 cm^{-1} (conjugated nitrile).

The infrared spectrum was identical in every respect with that of an authentic sample of cinnamylidene acetonitrile prepared according to the method reported by Vorlaender.² From the sodium carbonate washing, 0.71 g of benzoic acid (mp 121°) was obtained.

B.—A solution of II (1.70 g) in dry pyridine (5 ml) was cooled in an ice bath at 0–5°. Benzoyl chloride (1.82 g) was added dropwise with stirring. After stirring for 1 hr at the same temperature, the mixture was poured into ice water to give an oily substance, which on scratching with a glass rod was transformed to a crystalline solid, which was collected by filtration. The crude crystals were dissolved in ether and washed with 10% hydrochloric acid, 10% sodium carbonate, and then with water, at which time the temperature of the solution was maintained under 7° with ice. After drying over anhydrous sodium sulfate, the ether solution was condensed at diminished pressure and cooled in a freezing mixture (ice–sodium chloride) to give colorless crystals of IV: mp 78.5–79.5°; yield, 2.5 g (92%).

Anal. Calcd for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.07; H, 5.56; N, 5.19.

The infrared spectrum gave λ_{\max}^{KBr} 1759, 1739 cm^{-1} (shoulder); the ultraviolet spectrum gave λ_{\max}^{EtOH} , $m\mu$ (log ϵ), 237.5 (4.37), 325 (4.68).

When this reaction was carried out for 10 hr in pyridine–water (9:1) in place of dry pyridine, crystals of mp 78.5–79.5° were not isolated; however, when a small amount of ethanol was added to the resulting oily residue, which was allowed to stand at room temperature for several days, a crystalline solid separated. Purification by recrystallization from acetone gave colorless leaves: mp 157–158°; yield, 0.59 g (43%).

Anal. Calcd for $C_{18}H_{15}O_2N$ (V): C, 77.96; H, 5.45; N, 5.05. Found: C, 78.22; H, 5.49; N, 5.31.

Reaction of 1-Benzoyloxy-2-phenyl-1,2-dihydropyridine (IV).

A. Isomerization.—A solution of IV (0.4 g) in a small amount of ether (or ethanol) was placed in a sealed tube and allowed to stand for several days at room temperature. Colorless crystals were precipitated, collected, and crystallized from acetone giving colorless leaves of V: mp 157–158°; yield, 0.35 g (87%).

B. Aromatization.—A solution of IV (0.3 g) and a few drops of pyridine in benzene (6 ml) was refluxed for 1 hr. The solution was washed with 10% hydrochloric acid, and then with 10% sodium carbonate. The hydrochloric acid washing was neutralized with potassium carbonate to give an oil, which was purified by distillation to give a colorless oil: bp 140–150° (bath) (10 mm); picrate mp 157°, undepressed on admixture with an authentic sample of 2-phenylpyridine picrate (mp 157°);⁵ yield, 0.12 g (71%).

The sodium carbonate layer was acidified with concentrated hydrochloric acid to give a small amount of benzoic acid (mp 121°).

Reaction of Cinnamylidene Acetaldoxime Benzoate (V). A.

Thermal Decomposition.—Cinnamylidene acetaldoxime benzoate (V) (60 mg) was heated in an oil bath at 170° under reduced pressure (38 mm). The resulting yellowish oil was dissolved in ether, and the ether solution was extracted with 10% sodium hydroxide. From the sodium hydroxide extract benzoic acid was obtained. The sodium hydroxide insoluble fraction was washed with 10% hydrochloric acid, dried over sodium sulfate, condensed, and purified by distillation to give an oil, which was identified as III by the comparison of its infrared spectrum with that of an authentic sample.

B. Treatment with Alumina Column.—A solution of V (0.12 g) in benzene was submitted to alumina chromatography. Chloroform and then methanol were passed through the column. From the benzene effluent a small amount of III was obtained, and the methanol effluent was condensed to give pale yellow crystals. Recrystallization from water–ethanol gave pale yellow prisms, mp 158–159°, depressed to 130° on admixture with the starting material (V, mp 157–158°). This was identified as cinnamylidene acetaldoxime (mp 158–159°) by the mixture melting point test and the comparison of infrared spectrum with that of an authentic sample prepared according to the method reported by Vorlaender.²

Reactions of 1-Hydroxy-2-phenyl-1,2-dihydropyridine (II) with Acid and Alkali. A. With Hydrochloric Acid–Methanol.—

To a solution of II (0.5 g) in methanol (2.5 g) was added 20% hydrochloric acid (2.5 ml). After refluxing for 2 hr, the reaction mixture was allowed to stand at room temperature overnight. Yellow crystals precipitated and were collected and then purified by recrystallization from water–ethanol to give colorless prisms: mp 158–159°, which was undepressed on admixture with an authentic sample of cinnamylidene acetaldoxime (VI); yield, 0.03 g. The filtrate was concentrated, and extracted with chloroform. The chloroform extract was purified by alumina chromatography to give 0.03 g (7%) of III and 0.03 g of VI. The total yield of VI was 0.12 g (24%).

B. With 3 N Sodium Hydroxide.—A solution of II (0.5 g) in 3 N sodium hydroxide was refluxed for 1 hr. After cooling, the reaction solution was extracted with ether. From the ether extract 2-phenylpyridine (VII) was obtained: yield, 0.08 g (18%). The mother liquor was acidified with concentrated hydrochloric acid and extracted with ether. From the ether extract, the starting II (mp 130–131°) was recovered, 0.15 g (30%).

Cinnamylidene Acetaldoxime (VI).—To a solution of cinnamylidene acetaldehyde (bp 165–173°) (19 mm)² (1 g) in 50% ethanol (10 ml) was added hydroxylamine hydrochloride (1.25 g) and acetic acid (1.49 g) with stirring, and the reaction mixture was heated at 60–70° for 2 hr. After cooling, crystals which precipitated were collected by suction. Recrystallization from water–ethanol gave colorless prisms (mp 158–159°): yield, 0.18 g.

Anal. Calcd for $C_{11}H_{11}ON$ (VI): C, 76.27; H, 6.40; N, 8.09. Found: C, 76.16; H, 6.47; N, 7.99.

The ultraviolet spectrum gave λ_{\max}^{EtOH} , $m\mu$ (log ϵ), 238 (4.39), 316 (4.91), 382 (4.87).

Cinnamylidene Acetonitrile (III).—To a solution of VI (1.1 g) in pyridine (20 ml) was added benzoyl chloride (1.2 g). After stirring for 4 hr at room temperature, the reaction mixture was condensed *in vacuo*, and the resulting residue was dissolved in ether. After washing with 10% hydrochloric acid, 3 N sodium hydroxide, and then with water, the ether layer was condensed to give an oily substance, which was purified by distillation giving cinnamylidene acetonitrile: bp 106–107° (1 mm); yield, 0.8 g. The infrared spectrum exhibited a characteristic peak at 2212 cm^{-1} , (conjugated nitrile st) and was identical in every respect with that of the specimen obtained in the above run.

Reaction of 4,6-Dimethylpyrimidine 1-Oxide (XI) with Phenylmagnesium Bromide.—To a solution of 4,6-dimethylpyrimidine 1-oxide (XI) (4.6 g, 0.032 mole) in tetrahydrofuran (20 ml) was added dropwise 0.05 mole of phenyl Grignard reagent under ice cooling. After stirring for 5 hr at the same temperature, water was added and the resulting pasty yellow solid was washed with chloroform. After drying with anhydrous sodium sulfate, the combined solution was condensed *in vacuo* to give a dark residue, which was dissolved in acetic anhydride (30 ml) and allowed to stand overnight. After removal of acetic anhydride *in vacuo*, the residue was made alkaline with 10% sodium hydroxide to give a brown oil, which was extracted with ether. The ether layer was washed with 10% hydrochloric acid, and the hydrochloric acid layer was made alkaline with anhydrous potassium carbonate to give yellow crystals. Recrystallization from *n*-hexane gave 2-phenyl-4,6-dimethylpyrimidine (XII): mp 83°, which was undepressed on admixture with an authentic sample;⁶ yield, 2.5 g (45%).

Acid Hydrolysis of the Intermediate XIII.—In a fashion similar to that described above, 4,6-dimethylpyrimidine 1-oxide (XI) was treated with phenylmagnesium bromide. To the resulting residue was added 10% hydrochloric acid (20 ml), and the mixture was refluxed for 30 min and steam distilled. The distillate was extracted with ether. From the ether extract, 2.2 g of a colorless oil, bp 80–82° (25 mm), was obtained whose phenylhydrazone was identified as benzaldehyde phenylhydrazone by comparison with an authentic sample.

Registry No.—II, 3475-36-3; III, 14164-31-9; IV, 14271-18-2; V, 14164-32-0; VI, 14164-33-1; XII, 14164-34-2.

Acknowledgment.—The authors are indebted to Miss A. Sato, N. Nanjo, R. Oikawa, and Y. Tadano of this institute for the microanalysis and the infrared measurement.

(5) N. Goetz-Luthy, *J. Am. Chem. Soc.*, **71**, 2254 (1954).

(6) H. Haley and M. Maitland, *J. Chem. Soc.*, 3155 (1951).